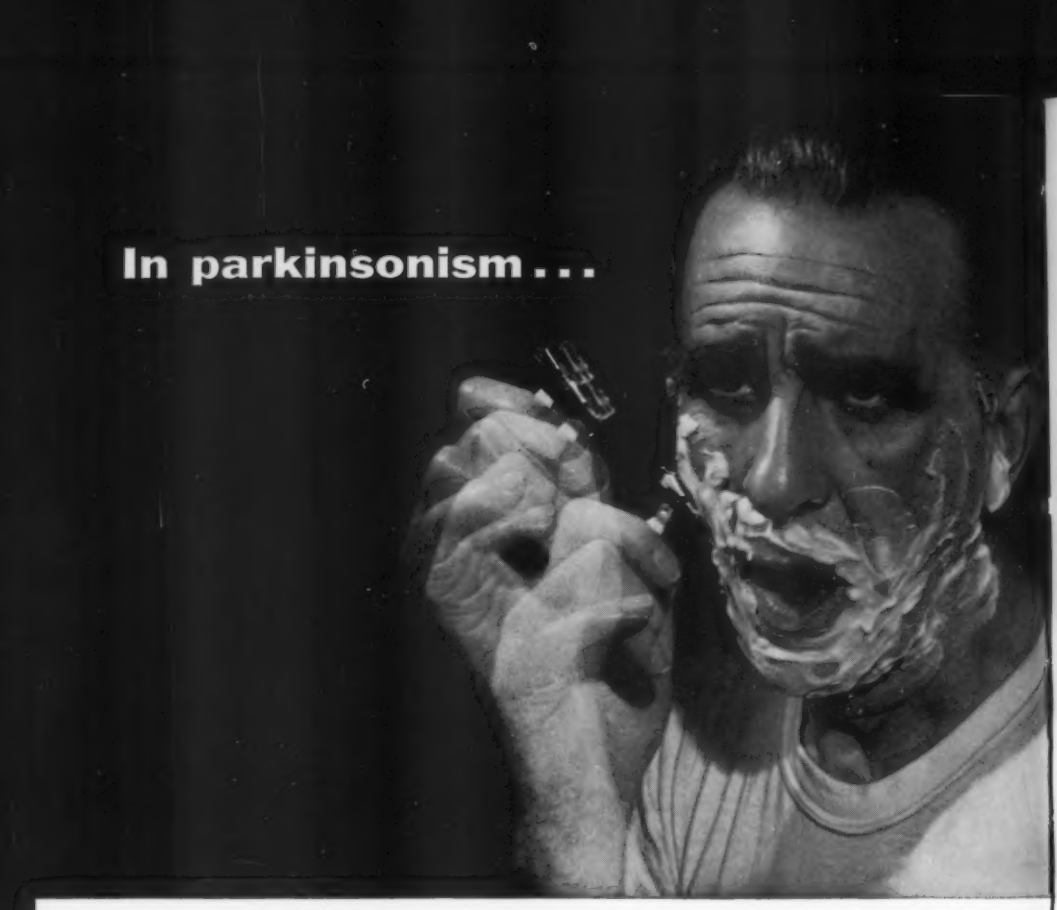
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

APRIL 1955
Volume 5 — Number 4



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1. Gallager, D. J. A., and Palmer, H.: New Zealand M. J. *49*:531 (Oct.) 1950. 2. Sigwald, J.: Presse méd. *59*:819 (Sept. 17) 1949. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. *247*:98 (July 17) 1952.

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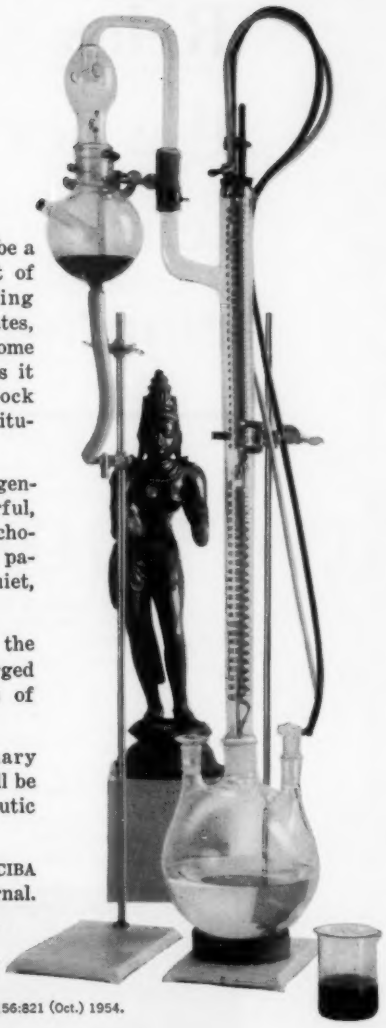

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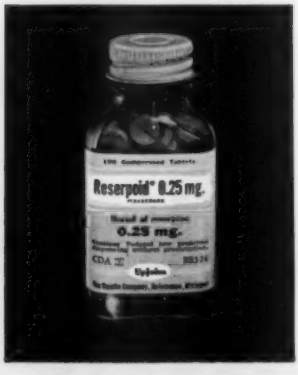

Volume 5 **Neurology** *Number 4*

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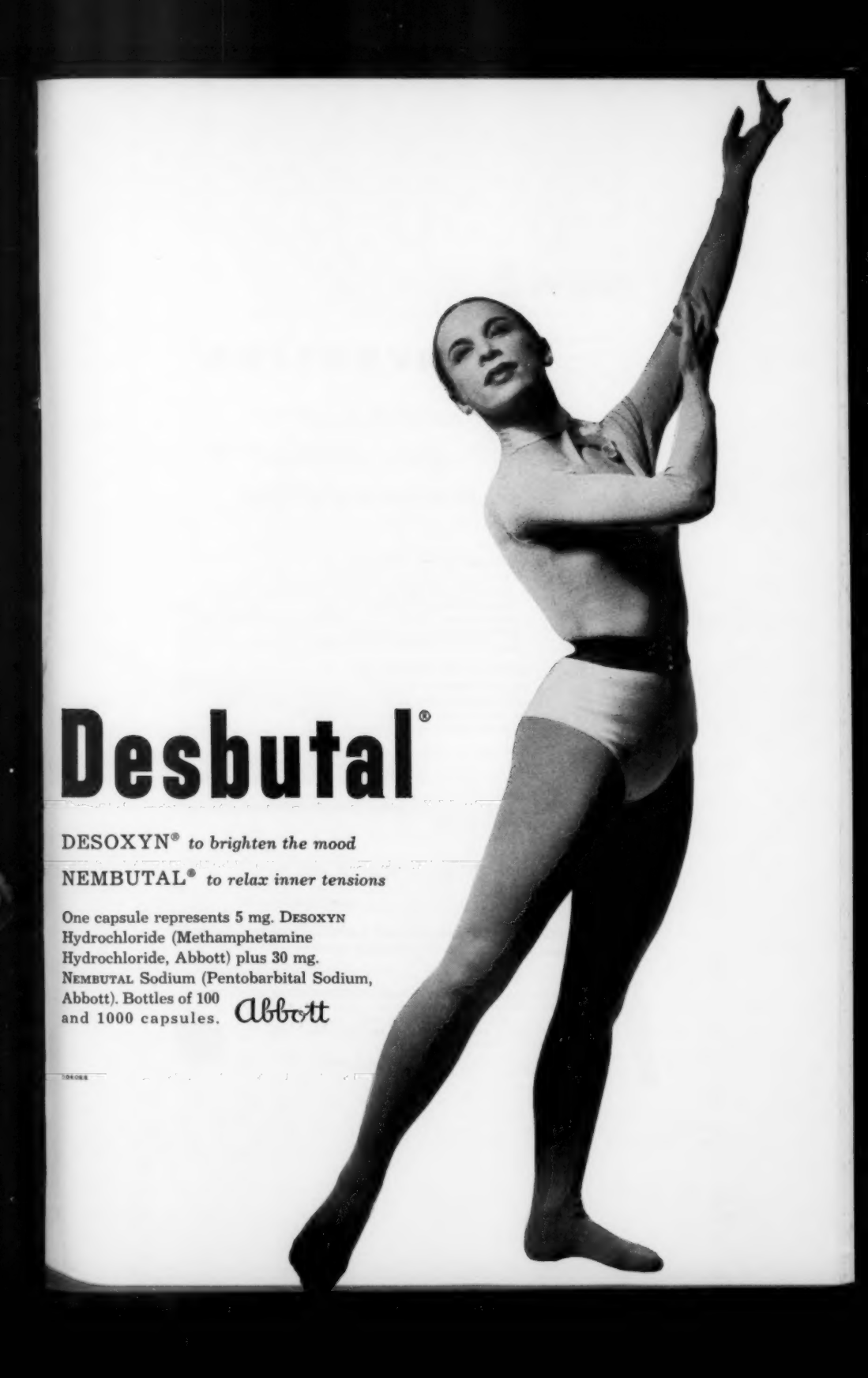
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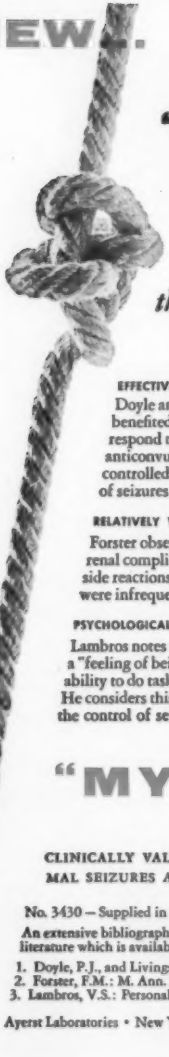

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1. Doyle, P.J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Forster, F.M.: M. Ann. District of Columbia *23*:137 (Mar.) 1954.
3. Lambros, V.S.: Personal Communication.

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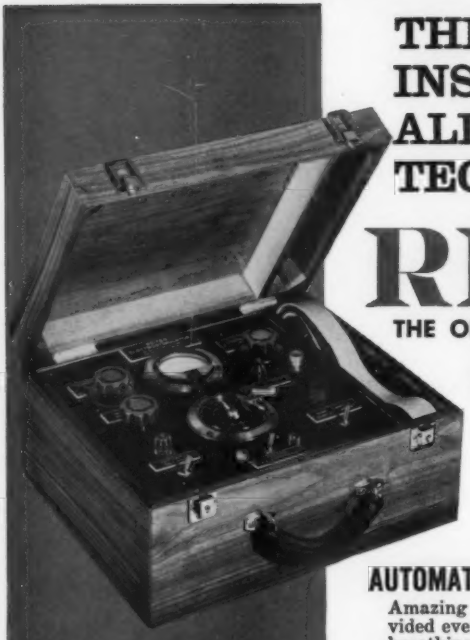

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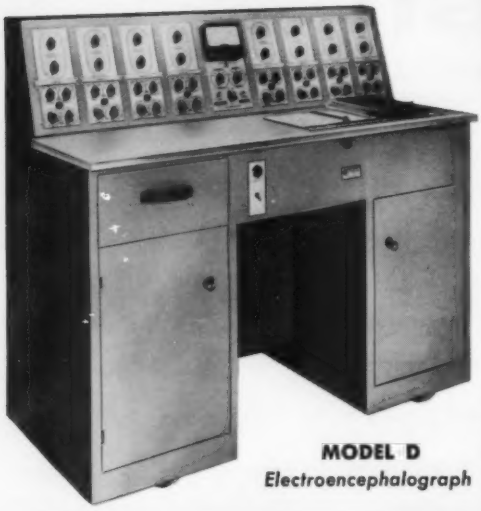

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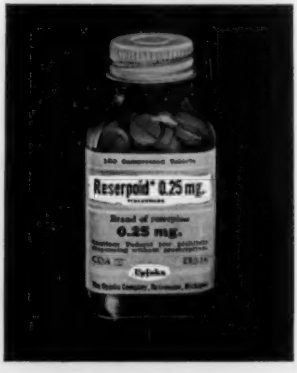

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Volume 5 Neurology Number 4

Western Equine and St. Louis Encephalitis

Preliminary Report of a Clinical Follow-up Study in California

Knox H. Finley, M.D., William Allen Longshore, Jr., M.D., Richard J. Palmer, M.D., Robert E. Cook, M.D. and Naomi Riggs, M.S.

MANY investigators have contributed to the knowledge of various aspects of the arthropod-borne encephalitides, including the etiology, epidemiology, natural cycle, control of the vector, and laboratory technics. Meyer[1] in 1930 first recognized an encephalomyelitis in horses in California and suspected a virus etiology. By 1932 he and his co-workers[2] suspected that the same causative agent produced an encephalitis in humans. Howitt,[3,4] in 1938, first definitely established that a Western strain of the equine encephalitis virus was the etiologic agent for human encephalitis occurring in the Central Valley of California. Muckenfuss and his co-workers[5] isolated a virus of the central nervous system of humans in an epidemic of encephalitis centering in St. Louis in 1933. This has since become known as the St. Louis neurotropic virus. This virus was isolated from a fatal human case in California in 1945 by Lennette.[6]

Hammon and Reeves and their co-workers,[7,8] working in the San Joaquin Valley in California and in the Yakima Valley in Washington, established that mosquitoes, primarily the *Culex tarsalis*, are the principal vector of the Western equine and St. Louis viruses. A mosquito vector helps to explain the seasonal appearance and the geographic distribution of these encephalitides in California, but the true reservoirs of infection are still not definitely known. Birds, domestic fowl, and certain mammal hosts are being studied currently as possible

From the department of neuropsychiatry, Stanford University Medical School, and the Bureau of Acute Communicable Diseases, California State Department of Public Health, San Francisco.
Original data were obtained in investigations supported in part by a research grant (B-442) from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.
Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 30, 1954.

reservoirs.[9] Reeves has stated that he considers men and horses accidental entries into the infection chain.[10]

Virologists have developed laboratory methods for etiologic diagnosis,[11] and entomologists and engineers have worked on problems of controlling the vector.[12] Few investigators, however, have reported on the long range, clinical aftereffects of these arthropod-borne viral illnesses. Bruyn and Lennette[13] published their observations of a few patients with sequelae. Two investigators in Canada[14] attempted to show in retrospect that some patients in mental hospitals may have had earlier infections of Western equine encephalitis. In general, clinical studies have been limited by two factors: either the small number of cases, or the lack of evidence that the etiologic agent for the acute illness was the Western equine or St. Louis encephalitis virus.

An epidemic of encephalitis in California in the summer of 1952 set the stage for a clinical study which is now in progress. Conditions existing during the winter and spring of 1951-52 seemed to be optimum for the rapid development of the *Culex tarsalis* mosquito. The snow pack in the adjacent Sierra Nevada mountains had been unusually heavy and the spring rainfall above normal. Furthermore, temperatures were moderate which favored early spring run-off of the snow packs and encouraged the propagation of mosquitoes.[15]

By early June 1952, entomologists had noted that the number of *Culex tarsalis* was much greater than normal. Efforts were begun at once to destroy and control the vector.

By the end of June, Kern County General Hospital had reported a large number of patients with an encephalitic syndrome. As this was unusual for this period, it became apparent to the state health department that an epidemic was in the making. It was predicted that there would be between 500 and 700 cases reported during the disease year. Local county health departments and family physicians were alerted. At California's request, the United States Public Health Service dispatched personnel from stations in various parts of the country to aid in this emergency. On August 1, the governor made emergency funds available to enable the state health department, through the Bureau of Vector Control, to finance an intensified program of mosquito control.[15]

By the end of the 1952 disease season, not only had there been 813 cases diagnosed clinically, but through the excellent cooperation of physicians, hospitals, and health departments (local and state), diagnostic blood specimens had been sent to the virus laboratory. As a result, 375 cases were confirmed as being caused by the Western equine and 45 by the St. Louis types of encephalitis virus. With mumps and recognized post-infection encephalitis excluded, there remained some 360 cases classified as "etiology unknown." This large number suggests as yet undiscovered virus etiologies.[16]

The laboratory tests used were the serologic studies for the presence of complement fixing or neutralizing antibodies. For this important immunologic investigation, two 15 cc. samples of whole blood were collected in sterile test tubes, the first specimen being taken as soon as possible after the onset of illness (acute specimen), and a second specimen was taken 14 to 30 days following the first (convalescent specimen). These specimens were sent directly to

FIG. 1. Location of clinics in California Central Valley. Encephalitis clinical follow-up study.

the virus laboratory.[17] Lennette and his co-workers[11] have stated that the in vitro complement fixation test is a better diagnostic tool than the in vivo neutralization test, since rises in titer are more readily detected by the former technic than by the latter. The complement fixing test is also quicker and cheaper than the neutralization test.

The comprehensive laboratory coverage identified the patients with Western equine and St. Louis encephalitis, and the completion of an epidemiologic history form provided information which made it possible to locate and contact the patients following their acute illness. Thus the essential data were available for initiating a study of the neurologic and psychiatric sequelae of these encephalitides. Funds for a six month pilot study beginning January 1, 1953, were made available by the director of the state department of public health. Stanford University Medical School then received a grant from the National Institute of Neurological Diseases and Blindness for the long term clinical follow-up study.

The study has now been in progress for 18 months. Thirteen clinic centers have been established in the Central Valley (figure 1) and 43 clinic sessions have been held. The original plan called for the examination of each patient every three to four months during the first year following the acute illness, semiannually for the next year or two, and annually thereafter. To date, this plan has been followed, but changes may be advisable depending on the number and character of the sequelae, the availability of patients for examination, and other as yet unknown factors. Of the patients who had Western equine or St. Louis encephalitis in 1952, 334 have been examined at least once and approximately two-thirds of these have been seen two or more times. This number constitutes 70 per cent of the cases which occurred in the 18 county areas where clinics have been held. Since approximately 10 per cent have been permanently lost to the study either through death or disappearance and another 10 per cent have moved and cannot be reached through the regularly scheduled clinics, there remain only about 10 per cent "theoretically available" who have not been examined. Actual unwillingness to participate in the study accounts for very few of these; the majority were unable to attend clinics for a variety of other reasons. A large measure of credit for the patients' favorable responses can be attributed to the enthusiasm and hard

work of those who started the pilot study and to the continued efforts of the local health units who assisted in setting up the clinics.

Because of the growing interest of the county health units, the community, and family physicians, and improved administration of the project, it has been possible to include in the clinics laboratory confirmed cases of encephalitis occurring during 1950, 1951, and 1953, as well as those who were ill in 1952. A total of 113 confirmed cases ill in other years have been seen in addition to the 334 who were ill in 1952. This brings the number of cases studied to 447.

Plans are under way to arrange for medical examinations by local physicians of those patients who live outside the areas in which special follow-up clinics are held. Also, consideration is being given to include all confirmed Western equine and St. Louis encephalitis cases occurring between 1945 and 1950. Records on these patients are available in the state health department, and since a sizeable proportion of patients ill as long ago as 1950 have been located, it seems probable that some of the patients ill prior to 1950 can also be found. As new cases occur, they will also be included in the study.

Blood specimens have been obtained at the clinics for the state virus laboratory. Specimens taken at intervals over a period of years will provide material for further study of various immunologic aspects of infection with the Western equine and St. Louis encephalitis viruses.

Lennette and his co-workers[11] have already reported that the complement-fixing antibody levels of infants tended to persist at the original level up to at least seven months, while the complement-fixing antibody level in older persons began to drop after the acute phase of the illness.

CLINICAL ASPECTS OF THE ACUTE ILLNESS

Encephalitis has occurred in patients ranging in age from a few days to 80 or more years. It has been reported that Western equine encephalitis virus in mothers at or near term crosses the placental barrier and infects the child prior to delivery.[18] However, St. Louis encephalitis has seldom been encountered in infants less than one year of age. Only three cases of St. Louis encephalitis in infants were reported in California during the last eight years. On the other hand, an unusually high proportion of Western equine encephalitis (usually from 20 to 30 per cent of each year's cases)[19] occurred in patients under one year of age.

The difficulties in establishing a diagnosis on clinical grounds have been pointed out by Kokernot and his co-workers,[20] who listed 20 other initial diagnoses made by attending physicians in cases in which laboratory tests ultimately proved the etiologic agent to be either the Western equine or St. Louis virus.

One of the most difficult differential diagnoses is poliomyelitis, which has a seasonal occurrence in the Central Valley of California similar to the arthropod-borne encephalitides. The appearance of lower motor neuron signs and bulbar symptoms are usually presumptive evidence of poliomyelitis. Other diseases manifesting similar clinical pictures and requiring careful consideration are mumps meningoencephalitis, tuberculous and coccidioidal meningitis, and postinfectious encephalomyelitis.

The definitive diagnosis of Western equine and St. Louis encephalitis rests with the serologic evidence of rise in titer of specific antibodies or the isolation of the virus.

Pending the results of immunologic studies, the outstanding clues are epidemiologic.[20] If the encephalitis patient is or recently has been in endemic areas and becomes ill during the "encephalitis season," Western equine or St. Louis encephalitis should be suspected. The interval between the inoculation of the virus and the first clinical signs is from five to 15 days.[21]

It is not possible to differentiate Western equine and St. Louis encephalitis clinically.[7,16,20,22] Clinical features of the acute illness vary with the age of the patient; however, fever and drowsiness are the most consistently observed symptoms among patients of all ages. Convulsions occur in from 75 to 80 per cent of infants less than one year of age, but in only 30 to 35 per cent of children one through four years. Restlessness and irritability are other prominent clinical features in both infants and children, and the children from age one through four have, in addition, headache, vomiting, and stiffness of the neck and back. In children, age five through 14, headache, fever, and drowsiness predominate. Usually fewer than 10 per cent have convulsions. Adults show drowsiness, lethargy, fever, stiffness of the back and neck, and almost always have severe occipital headaches. Stupor or coma occur in from 35 to 40 per cent of the adults. Disorientation and mental confusion are common, but convulsions almost never occur.[20]

The white blood count shows no consistent reaction to the virus infection. Spinal fluid shows a range of cells, usually from 50 to 200 per cc., although occasionally 1,000 or more may be present. Polymorphonuclear leukocytes predominate in the acute phase, and lymphocytes predominate in the recovery phase. Pleocytosis tends to be greater in children than in adults. Spinal fluid sugar and chloride values are usually normal in all age groups. Protein is either normal or slightly to moderately elevated, but seldom goes above 70 mg. per cent.[20]

Treatment in the acute phase is symptomatic. Although antibiotics have been given in many cases, there is no evidence which suggests that they change the course of the illness.

The most dramatic over-all clinical observation in all age groups is the sudden remission of symptoms and signs. Many patients admitted with convulsions or in stupor or coma recover, except for generalized weakness and fatigue, within five to ten days. In fact, many patients with less serious complaints are symptom free within three or four days.

Case fatality rates vary considerably depending on the bases used for computing rates and the degree of success in determining the etiologic agent. During 1952, of the 813 *clinically* diagnosed cases of encephalitis, 58 were fatal cases, giving a rate of 7.1 per cent. However, only nine of these were confirmed cases of Western equine and one a confirmed case of St. Louis encephalitis. This gives a case fatality rate for the 420 *immunologically* confirmed cases of only 2.4 per cent. At best, these rates are only approximations. They might be higher if in all fatal cases there were adequate autopsy material or paired blood specimens, or lower if all mild cases were recognized and accurately diagnosed. Of the ten cases who died of Western equine or St. Louis encephalitis in 1952,

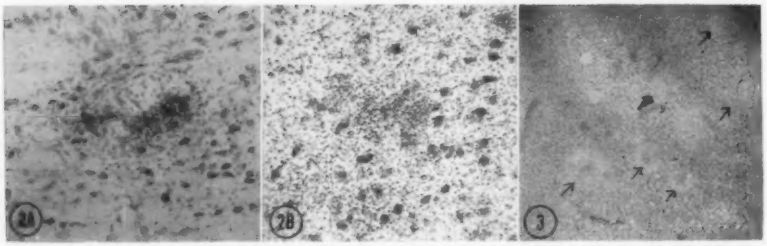

FIG. 2. *A.* Two nests of reacting cellular elements, mostly reacting microglial cells to a group of injured neurons. Region: pons. Case of Western equine encephalomyelitis. Nissel stain. *B.* A widespread area of predominantly microglial reaction. A confluence of several glial "nests" is apparent in the center of the photograph. Region: thalamus. Case of St. Louis encephalomyelitis. Nissl stain.

FIG. 3. Arrows point to pale spherical amorphous lesions interpreted as a late stage of what was originally an active reacting glial "nest." The necrotic remains of these glial elements appear as a residual core in the centers of some of the amorphous lesions. Region: cerebral cortex. Case of Western equine encephalomyelitis. Nissl stain.

six were 50 years of age or older. The others were not concentrated in any particular age group.

Studies of autopsy material[23] revealed that the histopathologic lesions were distributed throughout the central nervous system but primarily in the thalamus, striated body nuclei, pontine nuclei, purkinje cells, and molecular cell layers of the cerebellar cortex. Ganglion cells were involved in many different regions and layers of the cerebral cortex, although less frequently than in the above mentioned nuclei. A few ganglion cells in the dentate nuclei, the inferior olives, and the nuclei of the tegmentum of the brain were usually involved. Lesions in the spinal cord have also been described.[20,23,24,25] As it was not possible clinically to distinguish between Western equine and St. Louis encephalomyelitis, the same holds for the neuroanatomic material.

The neuron cell body appeared to be one of the primary points of attack, either singly or in groups of several (figure 2). Cellular response to the neuronal injury consisted of mononuclear cells, predominately microglia forming "nests" of varying sizes and densities, depending primarily upon the number of ganglion cells involved and the age of the lesion. Neutrophilic leukocytes were found in the younger appearing microglial "nests." Occasional microglial "nests" were found in the white matter of the cerebrum and cerebellum. Whether these were in relation to an isolated subcortical neuron, a blood vessel, or due to virus involvement of glial elements is a consideration for further study. One of the most striking lesions was a sharply demarcated, amorphous-like lesion, usually larger than the microglial "nest" (figure 3). These amorphous lesions appeared to develop in and about the microglial "nest" and often had the appearance suggesting lysis of the reacting cellular "nests" in their later stages.

POSTENCEPHALITIS SEQUELAE

Although the clinical follow-up study has now been in operation for a year and a half, it is too early for a detailed and definitive report. The material in this paper is limited to simple counts of sequelae, plus some general observations. "Sequela" refers to any neurologic

TABLE 1
NUMBER AND PERCENTAGE OF PATIENTS WITH SEQUELAE BY AGE GROUPS

Age at onset of illness	*Number examined*	*Number with sequelae*	*Percent with sequelae*
Under 1 year	98	53	54
1 to 4 years	54	19	35
5 to 14 years	78	20	26
15 years and over	217	50	23
Total	447	142	32

or psychiatric abnormality which seems to be attributable to encephalitis. These abnormalities range from a mild emotional disturbance to severe neurologic damage. No attempt has been made to classify sequelae according to severity, chronicity, or practical significance to the patient, nor to the lapse of time between the encephalitis and the follow-up examination. (This time interval ranged from three months to four years.) More detailed breakdowns will be prepared as more definitive data are collected and evaluated. These early findings are reported here with full recognition that later reports may enlarge, clarify, or even appear to conflict with these findings.

All data which follow are based on the total patients examined (447) and include patients who were ill in 1950, 1951, 1952, and 1953. Of the 447 patients, 142, or 32 per cent, had sequelae at the time they were examined. The frequency of occurrence of sequelae varied with age, as is evident from table 1.

Not only the frequency but also the types and severity of sequelae varied with the age of the patient at onset of the acute illness. Therefore, these can best be discussed by age groups.

PATIENTS UNDER ONE YEAR OF AGE

Infants seem to be particularly vulnerable to the Western equine virus. Not only is the number of cases in this age group higher than in any other, but infants develop the more serious neurologic signs, particularly convulsions, and more frequently are left with severe sequelae. Of the 98 infants examined, 53 had sequelae. Table 2 shows the numbers of infants examined by age groups and the numbers with and without sequelae. Sequelae fell roughly into three types: 1) convulsions, 2) behavior retardation, and 3) upper motor neuron signs. In infants, it is generally difficult to distinguish between mental retardation and delayed behavioral development. Behavior retardation is used here to include both. In the preliminary stage of this study, the measurement of behavioral development has been based primarily on the age at which certain behavioral characteristics appeared, such

TABLE 2
RELATIONSHIP OF SEQUELAE IN INFANTS TO AGE AT ONSET OF ACUTE ENCEPHALITIS

Age at onset	*Number of infants*			*Percentage with sequelae*
	With sequelae	*Without sequelae*	*Total*	
Less than 3 months	43	27	70	61
3 months to 1 year	10	18	28	36
Total under 1 year	53	45	98	54

TABLE 3
RELATIONSHIP OF CONVULSIONS DURING ACUTE ENCEPHALITIS TO SEQUELAE IN INFANTS BY AGE AT ONSET

Age at onset	Number of infants: With sequelae	Number of infants: Without sequelae	Percentage with sequelae
CONVULSIONS:			
Less than 3 months	39	20	66
3 months to 1 year	8	12	40
NO CONVULSIONS:			
Less than 3 months	4	7	36
3 months to 1 year	2	6	25

as sitting alone, walking, talking, and the acquisition of voluntary sphincter control. Upper motor neuron includes both pyramidal and extrapyramidal signs.

The presence or absence of convulsions during the acute illness was found to have a definite relationship to sequelae (table 3). Seventy-nine of the 98 infants had convulsions during their acute illnesses and 29 of these have had recurrences of convulsions. The recurrence of convulsions was frequently accompanied by the other types of sequelae. In addition to convulsions, 15 of the 29 had upper motor neuron difficulties and were also retarded in behavior. Four of the 29 had convulsions and were retarded, but showed no evidence of upper motor neuron damage. Two of the 29 had convulsions with upper motor neuron signs, but seemed to be developing normally in behavior. The remaining eight of the 29 had only recurrence of convulsions.

The 19 infants who did not have convulsions during their acute illnesses had fewer and less severe sequelae. None of them had convulsions or a combination of behavior retardation and upper motor neuron signs. Only six had sequelae of any kind; two of these were retarded in behavior and four had upper motor neuron signs.

The very young infants – those less than three months of age – were the most severely affected of any age group. As can be seen in table 2, sequelae occurred in well over half (61 per cent) of the infants ill during the first three months of life, but occurred in only about a third (36 per cent) of the infants who were ill between the ages of three months and one year. Furthermore, while older infants were likely to be affected by only one of the three types of complications, that is, convulsions, behavior retardation, and upper motor neuron signs, the very young often had more than one of these residuals. Of the 70 infants who were ill within the first three months of life, 14 of them had all three types of sequelae. Only one infant in the three to 11 months age group was similarly affected.

It seems safe to state that if an infant does not develop encephalitis until after he has reached the age of three months, his chances of recovering without severe sequelae are good. Furthermore, his chances of overcoming his difficulties are more propitious, as it was observed that the setback in development of older infants was frequently temporary.

Some of the infants have had only one convulsion since the acute illness. In

some, the convulsion has been accompanied by fever; in others it has not. A number of children had been placed on anticonvulsant therapy so the picture is not clear as to whether the one convulsion was an isolated incident or might have been the beginning of a series.

Thirty-one of the 98 infants examined showed behavior retardation. In approximately half (15 cases), the retardation was severe, and all of these infants had accompanying motor difficulties such as spasticity, rigidity, and weakness of the extremities. Sixteen others were mildly retarded and five of these had motor difficulties as well. Ten infants who showed no evidence of behavior retardation had mild motor difficulties. Eight infants had recurrence of convulsions without any apparent retardation or motor impairment. Chorea or athetosis had not been observed in these infants.

The kinds of behavior and neurologic difficulties found in this age group were readily observable for the most part. The major difficulty arose in determining whether the abnormality was attributable to the encephalitis or was due to some hereditary, congenital, or other neurologic disorder.

It was encouraging to observe that a few infants whose encephalitis had left them in a state of complete helplessness have shown remarkable development within two or three years, and have practically caught up to the level of behavior normal for their ages. Others with less marked difficulties have also shown considerable improvement and the remaining sequelae may eventually be of little practical handicap to the patients. There are a few others, however, who appear to have made very little progress. Two are institutionalized and four others are almost completely helpless and are being cared for at home. Three infants who have been seen in the clinics have since died.* In no case was encephalitis considered the direct cause of death (two died of pneumonia and one of "gastric enteritis") although all three children had severe sequelae following their encephalitis attacks.

PATIENTS ONE THROUGH FOUR YEARS

For purposes of convenience, all patients from ages one through four were grouped together, although the one year olds were more like the infants than they were like the two to four year olds, both in their response to the acute infection and in the sequelae which resulted. About 60 per cent of the one year olds had convulsions during the acute illness, as compared with 75 to 80 per cent among infants and about 15 per cent in children aged two through four. Fifty per cent of the one year olds had sequelae, as compared with 54 per cent among infants and 29 per cent in the children aged two through four. Three of the five children in the one through four age group who had recurrence of convulsions were one year of age at the time of their encephalitis. However, none of them had accompanying retardation as was common among the infants. The one child in the one through four year age group who was markedly retarded by the acute illness was 15 months of age when she became ill. This child, who was three years of age when last examined, has made remarkable improvement and the only sequela was delayed speech. This child had no recurrence of convulsions. One child who had convulsions was also irritable and had sleep disturbances.

*These cases are not included in the 10 reported deaths previously mentioned.

Summarizing the one through four year group as a whole, 19 of the 54 (35 per cent) children examined had sequelae. As already stated, five cases had recurrences of convulsions; one case had severe behavior retardation. Seven had evidence of upper motor neuron signs; one of these was also emotionally immature. Two children appeared to walk in a peculiar fashion. The other four were described as irritable, restless, nervous, emotionally unstable, and one had, in addition, an involuntary tremor. Athetosis associated with hemiparesis was observed in four of these children. There were no deaths in this age group.

PATIENTS FIVE THROUGH 14 YEARS

In infants and young children, most of the sequelae were demonstrable by objective tests and examinations. Only a few older patients had sequelae which produced abnormal neurologic signs. Most of the difficulties were of a more subjective nature, such as nervousness, irritability, restlessness, emotional lability, headaches, inability to concentrate, hyperactivity, sleep disturbances, speech impediments, and poor adjustment to school, family, and friends.

Because of the number of other conditions which are known to produce similar symptoms, it is not easy to ascertain whether these conditions were caused or aggravated by the encephalitis.

Of the 78 patients in the age range five through 14 years who were examined, 20 (26 per cent) had neurologic or psychiatric complaints. Five patients had abnormalities which produced neurologic signs such as hemiparesis and tremor. The other 15 had the types of symptoms described above.

Convulsions during the acute illness occurred infrequently (in about 8 per cent), but none of the children had shown evidence of recurrence of convulsions. One child had a mild chorea-like restlessness, accompanied by shuddering, tic-like movements of the head, neck, shoulders, and arms. Another child seemed mildly mentally retarded. There were no severely handicapped children in this group, and there were no deaths.

ADULT PATIENTS

The same kinds of difficulties in evaluation of abnormal findings in the five through 14 year olds were encountered in studying adults. An additional problem, which was more apparent in adults but not necessarily confined to this group, had to do with how soon the patient was examined following his encephalitis. It has been fairly well established through observations made thus far that there was often a prolonged recovery period, even though acute symptoms subsided rapidly. Many patients regained their strength slowly, were tremulous, continued to have headaches, tired easily, or were more irritable than usual for three to six months or even longer. These symptoms were undoubtedly sequelae of the encephalitis but, since in most cases the symptoms gradually subsided, they did not constitute permanent, chronic sequelae for most patients.

In later reports it may be possible to differentiate between early residuals and the more chronic sequelae of these patients. For this report, all abnormalities were grouped together, regardless of the length of time lapse between the illness and the examination.

Two hundred and seventeen adults were examined and 50 of them had some kind of symptoms or abnormal findings. More than half of these (28) complained of symptoms such as irritability, nerv-

ousness, headaches, "shakiness," inability to concentrate, and faulty memory. The neurologic examinations of 19 of these patients were negative. Hyperactive reflexes, tremor of hands and tongue, unsteady or irregular gait were observed in the other nine. Upper motor neuron signs were present in an additional 17 individuals who otherwise appeared quite normal. Of the remaining five, two had convulsions and three had psychotic symptoms and signs.

Probably not more than five per cent of the adults had sequelae which were sufficiently severe to be of any practical significance to the patients. In the cases showing paralysis or muscle weakness, only five were seriously handicapped, and in three of these five cases there was question as to whether encephalitis was the only diagnosis despite positive laboratory findings. In the two other patients with severe handicaps, the evidence favored an encephalitic etiology, although the patients' difficulties might be due to other pathology since both were in the older age group in which aging etiologies might be expected. In both cases, the sequelae were related to the cerebellar, extrapyramidal system and were expressed in unsteady, irregular gait. Both patients had scanning speech.

Two patients have developed convulsions since the acute illness. Neither had seizures during the acute phase, but both were stuporous and comatose. In one of these the encephalitic etiology seemed clear, but in the other case there were factors which need further evaluation. No patient had a postencephalitic parkinsonian syndrome, although one patient had developed an unusual type of respiratory tic.

There has been considerable interest among health department personnel and others about the possibility that encephalitis might have contributed to mental breakdowns in five patients and antisocial behavior in three others. In only one instance does this cause and effect relationship seem clear. One patient became psychotic during his acute illness and was hospitalized for a few months in a mental hospital. His mental illness cleared rapidly and he has remained well for two years. Four other patients were known to have been admitted to hospitals for treatment of mental illness. Two of these four had a history of emotional difficulties prior to their encephalitis and neither was hospitalized until some months after the encephalitis. It is questionable that the encephalitis had anything to do with their subsequent mental breakdowns. Information on the other two of these four patients was not adequate for any judgments to be made.

Three men, two of whom were seriously ill with encephalitis, subsequently committed criminal offenses. In two cases, the patients' illness with encephalitis was studied as a part of the patients' legal defense but in neither case was it considered significant in explaining the patients' behavior.

Only one adult patient who had been examined died. She was 68 years of age when she had encephalitis in 1952, and when examined in 1953 she had no sequelae. The cause of death was coronary thrombosis. A number of other patients have been reported to have died but, as yet, no attempt has been made to determine if encephalitis was in any way responsible for their deaths.

ELECTROENCEPHALOGRAMS

None of the patients in the study had an electroencephalogram during the

acute phase of the illness, since in most instances the patients were admitted to hospitals having services for communicable diseases and these particular hospitals (with one exception) did not have electroencephalographic laboratories. The earliest follow-up electroencephalograms were done six months after the acute illness. The longest interval between the illness and the electroencephalogram was about three years.

Electroencephalograms were obtained on 140, or almost one third, of the patients who were examined in the special clinics. Ninety-three, or 67 per cent of these were normal tracings; 16, or 11 per cent, were considered borderline; 31, or 22 per cent, were interpreted as abnormal. These percentages follow fairly closely those reported in published studies of normal control groups. The electroencephalographic readings have not as yet been correlated with the clinical findings.

DISCUSSION

The epidemic of arthropod-borne encephalitis (Western equine and St. Louis types) which occurred in the Central Valley of California in 1952 provided the incentive for studying the long range effects of these illnesses.

Both the Western equine and St. Louis encephalitis viruses produce antibodies in the serum which can be identified by complement fixation and neutralization tests. At present, these tests serve as the only method of making a definitive diagnosis. Pleocytosis and some elevation in protein is found in the spinal fluid, but these findings are of nonspecific diagnostic aid. The proportion of patients in this study group with abnormal follow-up electroencephalograms approximated the percentage found among normal control groups. There was no characteristic abnormal pattern.

These encephalitides affect both infants and adults. In patients of all ages, the acute illness is characterized by fever and disturbed consciousness varying from drowsiness through stupor and confusion to coma. Convulsions are common in patients under one year of age.

During the 1952 epidemic, there was a mortality rate of 2.4 per cent, including both Western equine and St. Louis types. Deaths were not concentrated in any particular age group.

Follow-up examinations made thus far indicated that sequelae were most numerous in the younger patients, especially those who became ill before three months of age, and particularly if convulsions were a part of the acute illness. No infant free of convulsions during the acute illness has subsequently developed convulsions. (The maximum interval between the illness and the last follow-up examination was four years.) Recurrences of convulsions were often associated with the more severe mental and motor complications. Many infants with mental or motor sequelae or both had shown progressive improvement with time.

Older children, five through 14 years, had a lower incidence of sequelae and these were less severe; 7 per cent had neurologic signs; another 19 per cent had subjective complaints such as nervousness and irritability. None of these children had convulsions.

Only two adults of the 217 examined had developed postencephalitic convulsions. One other patient had neurologic residuals. No patient had a parkinsonian syndrome attributable to encephalitis.

This study clearly establishes that, in determining the cause of convulsions in

the early weeks of life, one must consider acquired causes including neurotropic viruses. The assumption should not be made that, because an infant has convulsions soon after birth, these are due to birth trauma, or congenital and/or hereditary factors.

At this time, findings from the study indicate:

1. Infants less than three months of age who have an arthropod-borne encephalitis may have severe sequelae.

2. Children free from convulsions during the acute illness are less likely to have sequelae of any kind and are less likely to develop convulsions later.

3. Severe sequelae in adults are infrequent.

4. Most patients with sequelae, regardless of age, have shown a tendency to improve with time.

5. There is no evidence to date that either Western equine or St. Louis encephalitis produces parkinsonism.

The authors wish to thank the local health departments whose help in organizing and conducting the clinics has made this study possible. For their cooperation in obtaining the electroencephalographic tracings, we are indebted to the electroencephalographic laboratory and its director, Dr. Roger Scherb, of the Stockton State Hospital, to Dr. Ralph Gladen, Modesto, to Dr. Mark Zeifert, Fresno, and to Dr. Howard V. Petzold and the Sutter Hospital, Sacramento.

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Desoxyn Therapy for Nocturnal Seizures

A Preliminary Report

John Logothetis, M.D.

AMPHETAMINE SULFATE has been employed for several years to counteract the undesirable side effects of sedation in the therapy of convulsive disorders.[1,2] In 1937 Golla[3] noted that "pycnolepsy" in a seven year old girl could be controlled by amphetamine. Similar favorable results in petit mal epilepsy were reported by Livingston[4] and by Strauss.[5] The use of Desoxyn (methamphetamine sulphate) has also proved beneficial in the treatment of certain patients with major seizures.

The present study was undertaken to clarify these observations and to determine the value of Desoxyn in convulsive disorders. The results presented in this preliminary report indicate that this drug is beneficial in nocturnal epilepsy.

MATERIAL AND METHODS

Forty-six patients with convulsive disorders were studied while under Desoxyn therapy. They were selected without regard to age or sex. Each had been treated for several years in the seizure clinic of the University of Minnesota Hospitals without achieving adequate control. There was no progression of neurologic findings during this period. The convulsive episodes varied from one to five per month in half of the group and from five to 16 per month in the remaining half. Laboratory studies including skull roentgenograms, blood serology, blood sedimentation rate, and routine hematologic studies were within normal limits. Glucose tolerance tests were administered in 90 per cent of the cases exhibiting nocturnal seizures and in 50 per cent of those with daytime seizures. In all instances these determinations were within normal limits. Twenty-six patients were subjected to pneumoencephalography. These studies were normal in 22, while four exhibited diffuse cerebral atrophy. Forty-two patients were studied electroencephalographically.

In 20 patients, 90 per cent or more of the seizures occurred nocturnally. The remaining 26 patients experienced major, minor, psychomotor, or focal seizures almost entirely during the day. All subjects under study had been on previous medication for a minimum of two

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years. Ninety per cent were treated with Dilantin in an average dose of 3 gr. daily, accompanied by an average of 4.5 gr. of Mebaral. The remaining 10 per cent were treated with Mesantoin, Tridione, phenobarbital, Dilantin, and Mebaral in various combinations.

Desoxyn was added to the pre-existing medication in a dosage of 10 to 15 mg. in two to three divided doses. It was administered during the day to patients with daytime seizures, and in the evening and at bedtime to those with nocturnal seizures. The average duration of treatment was nine months and patients were re-evaluated at two to three month intervals. The total number of seizures during Desoxyn therapy was then compared to the number of seizures occurring during the same length of time prior to the institution of therapy with this drug.

SIDE REACTIONS

Desoxyn was well tolerated, with only a few mild, undesirable reactions. One patient complained of diarrhea and another of dizziness. Patients with daytime seizures frequently complained of insomnia, despite the fact that the drug was taken prior to 5 P.M. Only two patients with nocturnal seizures noted insomnia, even though Desoxyn was administered late in the evening.

RESULTS

Thirteen of the 20 patients with nocturnal seizures showed a decrease of at least 50 per cent in the number of seizures. Of the 26 patients with daytime seizures two received very minimal benefit, and one was completely relieved of petit mal seizures. Patients experiencing grand mal seizures during the day exhibited the greatest tendency to an increase in seizure frequency under the treatment. Half of the patients with daytime seizures experienced an increase in frequency, while only three with nocturnal spells showed such a tendency. The results are tabulated in table 1.

No correlation was evident between the effect of Desoxyn and the age or sex of the patient, the duration or etiology of the seizures, or the laboratory studies. Only the electroencephalographic findings showed any correlation with efficacy of the drug. Patients exhibiting patterns of bilateral synchronous two to six per second moderate to high voltage ac-

TABLE 1
THERAPY OF SEIZURES WITH DESOXYN

Results	*Nocturnal cases*	*Daytime cases*
Complete relief	1	1 (petit mal)
70–99% decrease in frequency of spells	5	0
50–70% decrease in frequency of spells	7	0
10–50% decrease in frequency of spells	1	2 (one petit mal)
No change in status	3	10
10–50% increase in frequency of spells	1	3
50–70% increase in frequency of spells	1	2
70–99% increase in frequency of spells	1	8
Per cent patients exhibiting over 50% decrease in frequency	65%	3.8%

tivity, spike and dome formation, or 14 and six per second positive spikes uniformly responded favorably to the addition of Desoxyn. Such activities were noted in seven patients with nocturnal seizures and two patients with daytime petit mal seizures. Twenty-five patients exhibited focal spikes and bilateral diffuse random abnormalities in the electroencephalogram. Fifteen of these experienced aggravation of symptoms, while seven did not respond to the therapy. All but five in this group were daytime cases. The remaining eight patients had normal electroencephalograms.

DISCUSSION

This preliminary report suggests that Desoxyn may be beneficial in the therapy of nocturnal seizures. The number of cases reported is not great and the period of administration of the drug is not sufficiently long to draw final conclusions. However, the diametrically opposite response of daytime seizures in comparison to nocturnal attacks offers evidence for the validity of these results.

The mechanism responsible for the effect of Desoxyn in nocturnal epilepsy is not readily explained. It appears possible that the differing physiologic states of sleep and wakefulness may offer different metabolic backgrounds for the action of the drug. Richter[6] suggested some connection between the increased frequency of nocturnal seizures and the elevated level of free acetylcholine during sleep. If increased acetylcholine levels were the responsible factor, it would then appear that the benefit from Desoxyn should result either from inhibition of the synthesis or liberation of acetylcholine, or from increased acetylcholine breakdown. There is as yet no evidence that amphetamine compounds have such an activity. Moreover the aggravation of daytime seizures by Desoxyn would be inconsistent with this action, since increased acetylcholine levels have been reported in epileptogenic foci.[7]

If one can assume that a release of a diencephalic focus from cortical control may be involved in the production of nocturnal seizures, then the beneficial effect of Desoxyn might be explained as resulting from a stimulating effect on the cortex,[8] producing lighter sleep[9] and more adequate cortical control over the diencephalon. Conversely, the aggravation of daytime seizures could then result from an activating effect on a cortical focus.

The experimental work of a number of investigators suggests that such a mechanism may be in operation.

Hypoglycemia of sufficient degree to produce electrical silence in the cortex, as well as rapidly developing severe hypoxia, have both been reported to produce convulsions by removing the subcortical structures from cortical control.[10–14] There is no indication, however, that sleep may precipitate convulsions in this manner. This would be expected since cortical depression during sleep does not result in cortical silence and, in addition, a decrease in hypothalamic activity, particularly hypothalamic-cortical discharges, accompanies the depression of the cortex.[10] Other experimental work,[15,16] however, indicates that diminution of cortical activity resulting from progressive hypoxia may activate and spread convulsive activity in the presence of an irritable subcortical focus. In these experiments spike activity appeared in the hypothalamus following injection of strychnine into this struc-

ture. This activity, together with the normal potentials in the cortex and thalamus, was reduced in amplitude when progressive hypoxia was produced. When all discharges were greatly diminished, synchronous bilateral spike discharges were then built up. Monopolar and bipolar recordings indicated that these discharges were subcortical in origin. Similar results were obtained when the strychnine focus was placed in the thalamus or caudate nucleus.

This experimental data indicates that cortical depression in hypoxia may release a diencephalic convulsive focus, even though electrical activity appears reduced in the diencephalon.

The above observations suggest a parallelism between hypoxic and nocturnal seizures in the presence of a diencephalic irritable focus. Acceptance of this mechanism does not exclude the possibility of nocturnal seizures resulting in some instances from a cortical focus. It is known that cortical convulsive activity in the electroencephalogram is more often detected during sleep[17] when a tendency for synchrony exists, as indicated by the large delta waves and sleep spindles. This activation appears to result from induced synchrony in an epileptic cortical area during sleep with many more neurons contributing to the convulsive potentials than during wakefulness.[10] In a similar manner it may be assumed that a released subcortical discharge during sleep, if insufficient to produce a clinical seizure, will induce synchrony in cortical potentials by recruitment mechanism. This type of hypersynchrony is capable of producing convulsions and may occur during wakefulness following stimulation of hypothalamic and other afferent pathways.[18] Such an action is suggested by the study of Dempsey and Morison,[19] in which recruiting potentials of large voltage were produced in the cortex of anesthetized rats as a result of stimulation of the dorsomedial region of the thalamus. It is also possible that the 14 and six per second positive spikes, reported by Gibbs[20] in a group of epileptics presumed to have diencephalic foci, do not represent simply distorted sleep spindles, but a type of induced synchrony.

Therefore, it appears that one common factor operates during sleep, tending to aggravate subclinical convulsive activity, regardless of the location of the focus. This factor is the tendency for hypersynchrony.

The bilateral simultaneous hypersynchrony appearing from a diencephalic focus probably represents an incomplete release phenomenon and appears more capable of leading to a seizure than the focal hypersynchrony about a cortical focus during sleep. Conversely, a deep-seated focus offers less possibility for a seizure during wakefulness, since it is inhibited by the corticothalamic impulses. We would expect, however, that subcortical discharges of sufficient strength to overcome the cortical inhibition, could induce a seizure even during wakefulness. This may explain the occasional daytime seizures in epileptics who otherwise have consistent nocturnal attacks.

It would then appear that sleep provides a better background for precipitation of a seizure, in the presence of a diencephalic focus than of a cortical focus.

On the basis of this experimental and theoretical data, Desoxyn may be considered to derive its value by activation of the cortex, producing more inhibitory corticodiencephalic impulses, and thus preventing the release of abnormal sub-

cortical discharges during sleep. Conversely, cortical activation by Desoxyn would induce greater convulsive activity in the presence of a cortical focus. Evidence exists indicating an activating effect of amphetamine compounds upon the cortex, particularly upon cortical epileptic foci.[9,21,22] Additional evidence was also demonstrated in this study by administration of Desoxyn to one patient during electroencephalographic recording. A left Jacksonian seizure was induced with high voltage activity on the electroencephalogram mixed with fast activity. This patient had undergone surgical removal of a section of atrophic frontoparietal cortex one year previously. Evidence was also obtained by the aggravation of seizures in almost all patients with focal spikes in the electroencephalogram.

No direct experimental evidence exists as yet that Desoxyn diminishes nocturnal seizures by increasing cortical inhibition of diencephalic irritative foci. Some evidence, however, was suggested in a patient with a 20 year history of nocturnal seizures. In addition, he was subject to frequent temper tantrums simulating rage reactions. An accompanying chiasmatic type visual defect also pointed to possible involvement of the hypothalamic area. Desoxyn was administered to this patient during a sleep electroencephalogram. Prior to the injection of Desoxyn, the electroencephalogram showed volleys of bilateral synchronous four to six per second high voltage waves on a background of nine to ten per second activity, associated with random negative spikes, slow waves, and 14 and six per second positive spikes. Following the injection of 10 mg. of Desoxyn into the tubing of a running intravenous infusion, the electrical activity became faster, lower in amplitude, and the spike activity was definitely diminished. This modification in the electrical activity was thought to represent limitation of the previously recorded convulsive activity.

The high incidence of synchronous high voltage bilateral electrical activity in the nocturnal cases was always connected with good therapeutic results in this series. This is suggestive of diencephalic abnormal activity which was reduced following cortical stimulation.

Additional support to the hypothesis of Desoxyn activity in nocturnal epilepsy is offered by the previously reported beneficial effect of amphetamine in petit mal seizures, which presumably are of diencephalic origin.[23,24]

SUMMARY

1. Twenty patients exhibiting nocturnal seizures were given Desoxyn (methamphetamine sulphate) added to their previous anticonvulsant medication. Thirteen of this group exhibited a significant decrease in the number of seizures.

2. Twenty-six patients with predominantly daytime seizures were treated in the same manner. Only one, a patient with petit mal seizures, received any benefit. Thirteen of the 26 experienced an increase in the number of seizures.

3. It is suggested that Desoxyn is effective in nocturnal and petit mal seizures through its cortical stimulating action, producing an inhibition of seizure discharges from the diencephalon.

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S. Weir Mitchell

I. S. Wechsler, M.D.

IT IS A GREAT PLEASURE for me to speak on this memorial occasion of a pioneer in American medicine who wrote his name so large in the annals of neurology. Here I stand in Philadelphia before a group of eminent neurologists and psychiatrists, some of whom may still recollect the great doctor, in the city which may be regarded as the cradle of American neurology, if not also the first center of medicine. Here lived and worked many pioneers who contributed to the growth of neurology. Without invidious comparison I would mention only a few, among them Charles K. Mills, one of the most outstanding of American neurologists, William G. Spiller, Charles W. Burr, Charles S. Potts, William S. B. Cadwalader, Francis X. Dercum, Charles H. Frazier, and Theodore H. Weisenburg. And so it becomes a little presumptuous on my part to record what has been better and more learnedly told by others, the life and the contributions of S. Weir Mitchell. And yet I am grateful for this opportunity to retell the story of one of our noted forebears in neurology and to draw some inspiration and perhaps a few parallels from the creative life of a doctor, a scientist, a poet and novelist, and, what appeals to me most strongly, a humanist.

It has always seemed to me that a great neurologist, like other great doctors, should be a little more than a specialist in his own field. Clearly the neurologist must be complete master of clinical neurology and have thorough grounding in neuroanatomy, neurophysiology, and neuropathology. He should have sound acquaintance with internal medicine and possess deep insight into psychiatric states. One cannot be a well-rounded clinical neurologist unless one is also a good psychiatrist, and it is not possible to practice the one without knowledge of the other. Whereas many psychiatrists, much to the detriment of progress, appear to have little interest in the structure and function of the brain, the practicing neurologist does not share this major disdain or the cavalier approach. The eminent neurologist should also be a scholarly doctor with genuine love of literature, including the great classics of all times, and have an interest in general history. Without an historic perspective, it may be added, there can be no culture at all. If, in addition, the neurologist be a man of wisdom and understanding with warm insight into human foibles and human folly and possesses the sense of humor which enables a man to laugh at himself, the desiderata for eminence are possible of fulfillment. I have always held to the view that a

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genuine sense of humor is a better index of intelligence, if not also of character and personality, than some of the current psychometric tests.

That noble breed of philosopher-poet-belle-lettrist-humanist-physician of days gone by has unfortunately and regrettably, though inevitably, almost disappeared. When learning took the place of knowledge and when knowledge itself was quite scant, many a scholar could take all of it for his domain. Roger Bacon did and so did Erasmus, who also knew how to praise folly. As knowledge accumulated it grew so vast that it became more and more difficult for one single mind to encompass all of it. With the tremendous development of science it is now almost impossible for one who would be master in his own field to cultivate neighboring fields – almost, but, I hope, not quite. Rabelais is adduced as an outstanding example but he was not a great doctor. Aside from his translation of the aphorisms of Hippocrates from Greek into Latin he contributed nothing to medicine. His fame rests on his creation of Pantagruel and Gargantua and on his wit and humor. The fame of Sir Thomas Browne derives from his *Religio Medici* and his discourse on Urn Burial, rather than from his achievements in medicine. Many physicians became famous as literary men only after they deserted medicine. Arthur Schnitzler grew to fame as a dramatist; Anton Chekhov as both novelist and dramatist; Conan Doyle challenged Poe and Gaboriau with his detective stories; Somerset Maugham wrote *Of Human Bondage*, a great novel; and Cronin practiced medicine for a time but left it to become a novelist. Sir Ronald Ross, who discovered the mosquito which carries the malaria plasmodium, wrote poems and novels and dramas, composed musical pieces, and even put his hand to sculpture and painting. In this country Oliver Wendell Holmes attained fame during his lifetime in both fields, but without aspersing his genuine merits it may be said, perhaps *sotto voce*, that he did not atain eminence in either.

S. Weir Mitchell excelled in both. While his poetry, with the exception of his *Ode on a Lycian Tomb*, has largely retired to honorable, if a little dusty, shelves, some of his novels can still be read with pleasure and profit. In the history of neurology his name is forever meritoriously inscribed.

Though much has been affectionately written about the life and creative achievements of Doctor Weir Mitchell, as he loved to be called, it is appropriate to recall, however briefly, why we are here to honor his memory. We of this generation may still learn instructively from first hand study of the great contributions of the pioneers in our field who, in little more than two generations, built the house of neurology in which we now live. One occasionally observes a tendency to derogate somewhat superciliously doctors of old as not modern, and so it is well to recall to failing memory the truism that not everything that is modern and recent is a contribution and not all great contributions are either modern or recent. It is good for every craftsman to know the history of his craft, and very good in that it conduces to beneficial modesty. A scholar's reward awaits those who would browse in the books and articles which came from Mitchell's pen.

S. Weir Mitchell was born on February 15, 1829. His grandfather, Alexander Mitchell, was a practitioner of medicine and his father, John Kearsley Mitchell,

was a good doctor who taught medicine at Jefferson Medical College, loved learning, and is reputed to have been a modest poet in his own right. Young Weir's early life and adolescence were uneventful, seemingly without evidence of special gifts to portend a brilliant future. However, he did become an avid reader and apparently acquired a taste for history. Before entering Jefferson in 1848 he attended some of his father's lectures. After two years of study he was graduated in 1850. With few honorable exceptions medical teaching in America was at a fairly low ebb and opportunities for advanced research such as existed in England and Scotland and especially in France and Germany were entirely wanting. And so young Doctor Mitchell went to Paris where he learned microscopy, spent about a year in Claude Bernard's laboratory, and came home with a microscope. On his return he set out to practice medicine in his father's office.

The first paper he wrote was on uric acid crystals. He soon became interested in vegetable poisons and snake venom, which led to the investigation of its alkaloids. His physiologic and toxicologic interest in the subject continued with interruptions for more than 50 years. As early as 1860 the Smithsonian Institution published a 150 page treatise on snake poisons. As late as 1901 he gave Noguchi a fellowship for the study of venom and so put the Japanese scientist on the road to fame. Twenty-five years after the beginning of his researches, Mitchell collaborated with Reichert on the action of venoms.

It was in 1862, when Mitchell became a contract surgeon in the U. S. Army and took up his studies on soldiers wounded in the war, that his neurologic career began. Surgeon General Hammond set up in Turners Lane a 400-bed hospital for nervous diseases and nerve wounds. There Mitchell collaborated with G. R. Morehouse and W. W. Keen, having made the acquaintance of the latter in 1860. While his main studies dealt with nerve injuries he was interested in the epilepsies and in chorea, especially postchorea paralysis. As early as 1864 he wrote with his two collaborators, *Gunshot Wounds and Other Injuries of Nerves,* wherein he described the syndrome of causalgia, ascending neuritis, and stump palsies. He also described reflex paralysis from remote wounds, a subject which Tinel, who was familiar with the French translation of Mitchell's book, studied during the first World War. The good doctor originally described erythromelalgia, which was known for a long time as Mitchell's disease. Nor did he fail to observe psychic phenomena in soldiers with nerve injuries and otherwise wounded soldiers. He even distinguished between hysteria, cowardice, and malingering.

His interest in neurology having been awakened during those early years, he pursued with zeal and industry the studies which found expression in innumerable important contributions. In 1869 he published a resumé of his studies on the cerebellum. These were based on animal experiments in pigeons, rabbits, and guinea pigs, the investigations dealing with ablations, freezing, irritation with cantharides, and penetrating wounds. He thought that the cerebellum was an organ reinforcing the spinal cord, an error to be sure, but not too violent a one. From 1870 to 1879 he published 39 papers and three books on neurology. In 1879 he became physician

to the Orthopedic Hospital, which was to include later the name of Infirmary for Nervous Diseases. It was then that he gave up general practice. Charles K. Mills became his protegé and in 1877 he helped his younger colleague to start a department of nervous diseases at Blockley. Mitchell wrote on neuralgia in locomotor ataxia, pain and weather, headache and eyestrain, facial tic, spastic paralysis, and the knee and ankle jerk. He not only studied the various forms of neuritis but the causalgia already alluded to, both as a symptom and a syndrome, the trophic disorders, and the physical and mental manifestations the result of amputation of limbs. He investigated minutely the cutaneous supply of nerves and noticed that the area of cutaneous loss did not correspond to the anatomic distribution, in which he recognized overlapping, and so was a forerunner of Henry Head. He employed massage and electricity in the treatment of nerve injuries, advocated nerve section and nerve stretching, and ice and sprays for the relief of local spasm and the reduction of pain.

The contribution which brought the good doctor his greatest fame as also his severest criticism was his rest cure, better known as the Weir Mitchell Treatment. Though he first described it at some length in 1873 in the *American Journal of the Medical Sciences*, he continued to contribute articles and books on the subject almost to the end of his days. He even embodied his pet theme in some of his novels. Critics not always animated by admiration and regard or honestly outraged by an affront to literary or scientific truth pounced on Mitchell unmercifully and held him up to ridicule. His books on *Lectures on Diseases of the Nervous System, Especially in Women; Wear and Tear,* and *The Nervous Woman* lent themselves particularly well to their hostile arrows, the points sometimes dipped in literary venom and aimed with unconcealed glee. He was ironically called a fashionable doctor and actually stigmatized as a charlatan. But one may observe in passing that the avidity with which some critics attack gifted men with original ideas is not always motivated by scientific ardor or passion for truth. To which may be added the observation that critics can be and often are more sensational than authors and that some indulge a human failing in the vain belief that they can increase their own stature by cutting down that of others.

It is true that the rest cure has lost much of its reputation as time marched on, but it is equally true that the kernel of truth which it embodied is still bearing fruit. Conceding that the theory underlying the treatment has lost its validity in the face of advancing knowledge, it will serve a more useful purpose to stress the very genuine contribution which Mitchell did make. Without intended offense, it may be said that much of what passes for science in modern psychiatry will probably turn out to be no science at all, and that what is now pontifically acclaimed as profound psychology may turn out to be plain gibberish and become the butt of future critics. All of which, perhaps as a non-sequitur, does not prevent people from writing volumes about things which can be better said in paragraphs; it merely confirms the dictum of *Ecclesiastes* that of the making of books there is no end.

The very important contribution of Mitchell was his insight, though not quite so expicitly stated, into the role of the emotions in illness in general and in

the neuroses in particular. The evidence of his recognition of the importance of psychic factors in disease consisted in his efforts to influence the minds of his patients. Charcot, the father of modern psychopathology, gave expression to the idea by means of hypnosis and suggestion; Binswanger, too, stressed the importance of the emotions; and George Beard, in this country, coined the word neurasthenia in 1869. Mitchell, it may be recalled, also wrote on dual personality. This profound insight into human motivation, which incidentally finds expression in what may be called his psychiatric novels – *Constance Trescott, In War Times, Characteristics, and Dr. North and His Friends* – almost marks him, without offense to his memory, as a psychoanalyst or at least as a therapist with analytic insight into human behavior. He had no knowledge, of course, of the libido, orificial erotic complexes, or the edipus situation; but it may be asserted without grave fear of contradiction, that Sophocles too did not set out to write a sex drama when he composed *Oedipus Rex* and Shakespeare did not create *Hamlet* to give literary proof of the existence of the edipus complex.

Lest these few remarks convey the erroneous impression of hostile criticism, may I say that I am not unfriendly to analysis and I yield to nobody in my appreciation of the great contributions of Freud and my regard for the profound insight into unconscious human motivation which he vouchsafed. One need not, indeed must not, abdicate reason when dealing with medicine as a science, nor in practicing the psychiatric art become the slave of a tool instead of its master. A great deal of what Freud said can be rejected with good reason, and one can only do grave injustice to his original contributions of permanent value by swallowing whole and uncritically much that is scientifically indigestible. One must ever beware of seductive language and constantly remember that palatable literary composition and even beautiful writing can conceal some very bad thinking.

There is one other field in which Mitchell may with permissible interpretation be credited with some pioneering insight. I refer to the word psychosomatic, a confusing shibboleth which, in its true meaning, merely represents a point of view and not a medical specialty, certainly not a medical science. It is quite clear that our good doctor was not aware of the theory underlying what now euphemistically passes for psychosomatic medicine and could not formulate it in modern terms, but he practiced it just as people in ordinary conversation often use a metonymy or synecdoche without being aware of the fact or knowing how to define either word. Without deprecating the subject, because there is in it a kernel of truth capable of bringing forth valuable fruit, one may more than diffidently call attention to the frothy shell which envelops the kernel. Unfortunately it is a common human failing to mistake theory for fact and to bridge with words gaps in knowledge which science cannot fill. There is also the quaint notion, somewhat akin to a minor delusion, that to coin a word is to create a fact. With apology to sensitive souls, this is neither good medicine nor good science.

If the exponents of psychosomatics are sometimes asked to define the word or are merely questioned, "How do you know?", they are somewhat hard put to reply. The fact is that the word is merely a modern formulation of the old

body-mind idea which has been scholastically debated by doctors and philosophers and theologians for centuries. When the ancient Greeks coined the word hysteria to explain the emotional havoc ostensibly caused by the peregrinations of the womb, or melancholia to indicate the psychosis caused by black bile, or hypochondria to show how something below the cartilages gives rise to a somatic delusion, they spoke in psychosomatic terms. They erred obviously, as we often err today, but the concept was there none the less. What is important in the modern formulation is the observation that bodily disease can cause mental and emotional disturbances and that continued anxieties, tensions, frustrations, and conflicts can ultimately express themselves in bodily disease. Assuming the correctness of the theoretic formulation, its truth is not established by endless reiteration of the theory or repetitious presentation of unconvincing case reports. What the neurologist, who is convinced that there can be neither function without structure nor structure without function, wants to know is how the disturbance comes about and what structures are involved. What are the physiologic or biochemical processes? What have the brain, the hypothalamus, the ascending and activating reticular system, the vegetative nervous system, the endocrines to do with the reciprocal reactions labeled psychosomatic? Until science provides the answer, the psychosomatic point of view will continue to express an old idea or a modern theoretic concept, a hopeful one to be sure, but still only an idea. Weir Mitchell, I think, had the idea.

It is conceded that, in addition to being an active clinician, Mitchell was also a good scientist. But it may be well to inquire, in view of the loose way in which the word scientist is frequently used, what characterizes the scientist. To be a true scientist one must possess absolute intellectual integrity, unquenchable curiosity, the capacity for objective criticism, courage to maintain and defend one's views, obsessive persistence in the pursuit of problems, and almost demonic ability to work. The last has been defined as the infinite capacity to take pains. However, important as all these characteristics are, what makes a truly great scientist, as it does all men of genius, is the gift of seeing new relationships. This alone makes for originality. While many do scientific work and often make valuable contributions few are endowed with imagination, with the poetic spark or the ability to dream, all so necessary to discovery of relationships previously unsuspected. One may conclude that, whether or not Mitchell was a great scientist or a man of genius, he possessed in good measure some of the qualities of both.

Weir Mitchell was not a cloistered scholar, but he loved learning and he loved books. Early in his medical career he came to know Billings, who laid the foundation for the growth of the Surgeon General's Library and initiated the *Index Medicus*. Like Osler, Mitchell showed interest in medical history and he searched out first editions and rare medical books for the library of the College of Physicians of Philadelphia. In 1891 he gave an address on "The History of Instrumental Precision in Medicine." Love of learning, in my opinion, is greater than learning. With all due respect for scholarship, some who are only scholars, in that they know everything others have said without saying anything original themselves, occasion-

ally show pride akin to arrogance; which is only a little less distressing than the arrogance born of ignorance. Love of learning begets admiration, which in turn begets modesty.

Despite the fact that both Jefferson and the University of Pennsylvania rejected him early in his career when he was a candidate for a professorship, Mitchell was a teacher. Mills, Cadwalader, Throckmorton, Beverly Tucker, and Noguchi were really his pupils. While Pepper and Osler, and perhaps Pepper more than Osler who soon left for Hopkins, are credited with making the University of Pennsylvania Medical School a great center, Mitchell contributed in many ways to its growth. He had great capacity for friendship and he counted among his friends Pepper, Billings, Osler, Welch, Holmes, William James, and many others. Being a Philadelphia aristocrat of Virginian lineage who knew how to eat cherries with pits at formal dinners, he advised that the young Canadian doctor whom he recommended for the professorship in medicine be subjected to the test of polite dining. Fortunately Osler passed the test with credit to himself and no disgrace to Mitchell. Think what American medicine owes to a cherry pit.

It would take too long to enumerate the many honors, including honorary degrees, which came to Mitchell. When the American Neurological Association was organized in 1875, he was elected the first president but he declined to serve. Curiously, it was not until 1909 that he became president of the association. In 1884 he was elected president of the Philadelphia Neurological Society. Jefferson, as if to atone for its failure to accept him as professor many years before, conferred an honorary degree on him when he was 81 years of age. His long productive and creative life came to an end on January 5, 1914, just six weeks before he reached the age of 85.

And so we come to the end of our story of S. Weir Mitchell, the neurologist. When he became a doctor in 1850 medicine was at a low level and neurology, with honorable exceptions, was practically without status as a discipline. Scientific neurology according to Neuburger only began in 1820 with Bell and Magendie. Romberg wrote the first comprehensive textbook of neurology in 1846. Clinical neurology was the stepchild of medicine and a neglected urchin in psychiatry. It actually began with Duchenne de Boulogne and Broca and Charcot, with Erb and Westphall, who in 1875 became the first professor of neurology in a German university, and Jackson and Gowers, and a host of other men of eminence. They described and classified the clinical entities as we know them today and brought order out of clinical confusion. Mitchell belonged to that galaxy of neurologists. Many American neurologists of eminence followed him as American medicine came of age, but it was he who truly pioneered in this country. Combining in himself, as he did, the poet, the novelist, the doctor, the neurologist and psychiatrist, he was in the true tradition of the humanist, a man of unique stature. What more can contemporaries demand or posterity record?

Epidemiologic Investigations of Amyotrophic Lateral Sclerosis

2. Familial Aggregations Indicative of Dominant Inheritance Part II.

Leonard T. Kurland, M.D., Dr.P.H. and*
Donald W. Mulder, M.D.†

THE first part of this article was published in the preceding number of this journal. The observation of considerable familial aggregation of cases of amyotrophic lateral sclerosis on Guam has led to the present study. The review of the literature for the past 100 years revealed 18 extensive pedigrees compatible with dominant inheritance. The view held by most neurologists and recent investigators to the effect that amyotrophic lateral sclerosis is not hereditary was also presented.

OUR OWN DATA. PEDIGREES

Six pedigrees will be presented; in three the genealogy was traced intensively. Five of the families described have resided in the upper midwestern states for several generations and are of English, German, or Scandinavian descent. One family of Irish descent arrived in midwestern United States about the middle of the last century.

C Family. The patient, who is referred to as the propositus in the pedigree (figure 15A, figure 15B, shows the code for pedigrees in figures 15A, 16, 18, 19, and 20) and is designated by an arrow in the figure, was a 57 year old white farmer from Iowa who first visited the Mayo Clinic on March 21, 1953, with the chief complaint of quivering muscles in the left calf of one month's duration and intermittent mild stiffness and soreness of his arms for two years. He stated that two older siblings, a maternal aunt, and two cousins had died of "the creeping paralysis."

The neurologic examination revealed muscle fasciculations present in the left lower extremity, most marked in the quadriceps femoris muscle. There were also occasional fasciculations over the left upper part of the abdominal wall and rare fasciculations in both biceps brachii. The electromyogram showed evidence of denervation in the left anterior tibial and calf muscles. Fasciculations were noted in the right anterior tibial and left biceps brachii. Fibrillations were noted in the left anterior tibial and left calf muscles only.

Eight months later, the patient was again examined (this time at his home), and at our request other members of his family were present and were examined. The patient then had a marked flaccid paralysis, with obvious muscle

A summary of this report was presented at the sixth annual meeting of the American Academy of Neurology in Washington, D. C., April 30, 1954.

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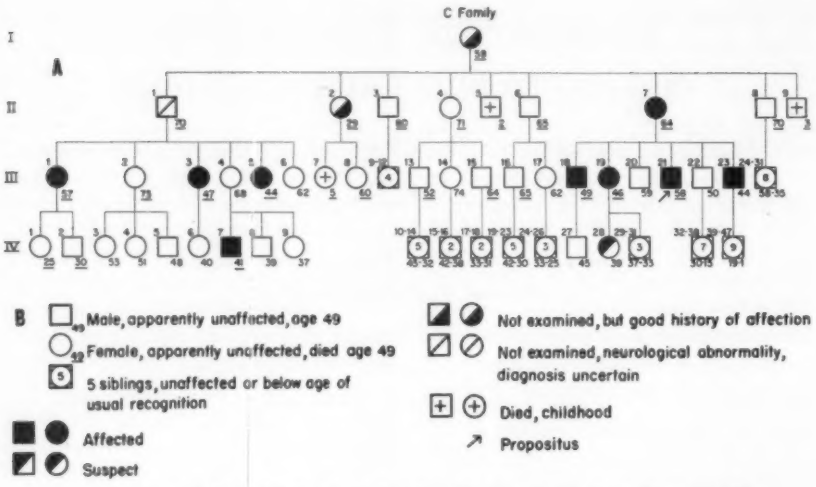

FIG. 15. *A.* Pedigree of C family. *B.* Code for pedigrees in figures 15, 16, 18, 19, and 20.

atrophy, of the entire left lower extremity. Only occasional fasciculations were seen in the left lower extremity, although they were now obvious in the other three extremities. There were also moderate weakness and slight wasting in all muscles in the left upper extremity and slight weakness in the right hand.

Two months later there was further progression, with advanced flaccid paralysis and muscle atrophy in the left lower extremity. There was moderate weakness in the left upper extremity, most marked in the hand, with wasting, especially in the intrinsic hand muscles. There was slight weakness in the right hand. Occasional fasciculations were present in all but the left lower extremity; the Babinski response was now present on the right and absent on the left. There were as yet no signs or symptoms referable to the cranial nerves. The sensory examination gave normal results.

In April 1954 the patient succumbed to bronchopneumonia. No necropsy was performed.

The patient had five siblings. Two of the older siblings (III-18, III-19) had died of progressive muscular atrophy. A sister (III-19) was a 45 year old housewife who had been seen at the clinic on May 6, 1937. She had been essentially well until one year before when she had noted weakness in the left foot. On examination she was found to be alert and cooperative and to have moderate dysarthria. There were muscle fasciculations and weakness in all four extremities, the tongue, back, and pectoral muscles. Muscle atrophy was evident in the tongue and in all four extremities, especially on the left side. Coordination and results of sensory examination were normal.

In June 1937 III-19 wrote that it was very difficult for her to eat and talk because "my tongue won't work and my throat seems to fill up." By September her local physician reported "much difficulty in talking and swallowing; left leg paralyzed and both arms practically out." She succumbed in November 1937, about 20 months after the onset of symptoms.

The older brother (III-18) of the propositus was a farmer who in November 1937, at the age of 48 years, noted dysarthria and dysphagia and later nasal regurgitation. His right hand became weak and wasted; later his left hand became weak and wasted. Vision, sensation, and coordination were normal. He had no involvement of his legs and was said to have plowed his farm two weeks before his death. He remained mentally alert until his terminal illness, which was reported by his local physician as respiratory infection. He died eight months after the onset of his symptoms.

A younger brother of the propositus (III-23) was examined at home on December 4, 1953.

Nine months previously, he had noticed the onset of occasional muscle twitchings and a vague numb feeling which began in the right leg and later spread to the other limbs. He had noted no actual weakness. In the last ten days, muscle quivering had occasionally been present in the face.

On examination, occasional muscle fasciculations were seen in right calf muscles. The Babinski response was present on the right but absent on the left. Otherwise, the results of neurologic examination at this time were negative. III-23 was seen by his local physician in April 1954, and was reported to have widespread muscle fasciculations, including fasciculations of the facial muscles, and moderate muscle atrophy in the shoulders, in addition to the findings of slight atrophy and spasticity in the lower extremities.

Two other siblings of the propositus (III-20 and III-22) had no neurologic complaints and on examination showed no abnormal neurologic signs.

A niece of the propositus (IV-28, a 39 year old housewife), the daughter of patient III-19, was also examined. She complained of nervousness and recently the presence of occasional muscle twitchings. She was examined on December 4, 1953. Aside from a moderately hyperactive left brachioradial muscle-stretch reflex (as compared to the right) and possibly some fasciculation of the tongue, no abnormality was noted on the neurologic examination.

Several other members of the family were examined (IV-8, 9, 29, 33, and 34). No abnormality was noted in any of these persons.

Further inquiry brought forth a number of histories which, in view of the apparent familial form of the disease and this family's intimate acquaintance with the symptomatology, are presumed to be a form of amyotrophic lateral sclerosis. Also, further inquiry from the family physician, who had known the family for more than 40 years, substantiated the family's impression that II-7, III-1, III-3, III-5, and IV-7 had died of the same type of paralysis as found in the offspring of II-7.

The history obtained from the family and the physician thus revealed the following cases and suspect cases.

I-1, maternal grandmother of the propositus, died in 1887 at the age of 58 years of a "creeping paralysis" of two to four years' duration. She was in a wheelchair during the last year or so.

No information regarding her siblings or parents could be obtained. She had nine children, seven of whom survived to adulthood. Of these, two died of "creeping paralysis."

II-2 died in 1882 at the age of 29 years, after an illness of "creeping paralysis" of two years' duration.

II-7, mother of the propositus, died in 1931 at the age of 64 years, following an illness of two years' duration characterized by progressive paralysis and muscle wasting, dysarthria, and dysphagia. She was in a wheelchair during the last year of her illness. Aside from II-1, all other offspring of I-1 who survived to adulthood did not develop any progressive paralysis. As far as we know, their children and grandchildren have also remained free of any progressive paralysis.

Of special interest are II-1, who died of a "stroke" in 1921 at the age of 70 years, and his descendants. This man had six daughters, three of whom died of "the paralysis." III-1 died in 1934 at age 57 years. Her most prominent symptom was progressive paralysis which began in the legs and lasted about 18 months.

III-3 died in 1936 at age 47 years, after a progressive wasting paralytic disease of about 18 months' duration.

III-5 died in 1938 at the age of 44 years. "Her wasting and weakness began in both arms and the chest. She died because of difficulty in breathing about 18 months after she became ill."

The offspring of these three patients are as follows:

IV-1 died following an acute infection at age 25 years.

IV-2 committed suicide at age 30 years.

IV-6 is apparently well at age 40 years.

The only definite case in generation IV is that of IV-7, whose mother (III-4, age 68 years) was examined and has no significant neurologic disorder.

This patient (IV-7) died in 1948 at the age of 41 years. His symptoms were dysarthria, dysphagia, progressive weakness and wasting of his hands, and weakness in the left leg. His first symptoms were those of progressive weakness and wasting in his left hand and shoulder muscles.

As a result of this disclosure of 12

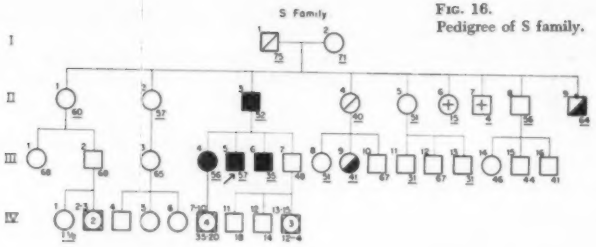

FIG. 16.
Pedigree of S family.

cases in four generations in this family, we inquired about other familial aggregations of cases of amyotrophic lateral sclerosis from the staff of the section of neurology of the Mayo Clinic, and several members were able to recall such cases in which at least one other family member was affected. By postal inquiry and visits to the families, it was possible to obtain sufficient data to develop several additional pedigrees.

S Family.—The propositus in this family was a 55 year old white barber who registered at the clinic on April 28, 1953, with the chief complaint of progressive painless weakness and intermittent "numbness" of the right foot and leg. He had been essentially well until five months previously, when he noted occasional "numbness" and slowly progressive weakness of the right foot and leg.

The patient reported that his father died of a "muscle dystrophy" at age 52 years. A younger brother, aged 34 years, and a sister, aged 56 years, he reported, had died of the same disease (figure 16).

On examination, the cranial nerves were normal except for slight weakness in the movement of the tongue. There was moderately advanced weakness in the right lower extremity with atrophy and occasional muscle fasciculations. In the left lower extremity, there was slight weakness, no detectable atrophy, and occasional muscle fasciculations. There was no Babinski sign. Co-ordination, memory, and results of sensory examination including vibration and position were normal.

Laboratory examination revealed normal hemoglobin, erythrocyte and leukocyte count, and negative Kline reaction.

Cerebrospinal fluid showed negative Kolmer and colloidal gold, 2 lymphocytes, 38 erythrocytes, 75 mg. protein per 100 cc., 66 mg. sugar per 100 cc., and 726 mg. chlorides per 100 cc. Dynamics were normal.

Electromyogram disclosed fibrillation potentials and reduced motor unit potentials in both legs compatible with chronic lower motor neuron disease. There were occasional fasciculations noted in the left arm.

The patient was reexamined at his home by one of us (Kurland) eight months later. At this time he was confined to a wheelchair with a complete flaccid paralysis of both lower extremities. There was moderately advanced flaccid paralysis of the right upper extremity, with atrophy and fasciculations. There was slight weakness of the left shoulder and hand with slight atrophy and fasciculation in the muscles of the left shoulder girdle and slight atrophy in the left hand. Dysarthria and tongue weakness were graded as minimal. The muscle-stretch reflexes in the upper extremities were diminished on the right, slightly hyperactive on the left; they were absent in the lower extremities. There was a Hoffmann response on the left; there were no Babinski signs. Results of sensory examination and coordination were normal.

The patient succumbed to respiratory infection in April 1954 (17 months after onset). Necropsy was carried out by Dr. William V. Knoll of Duluth, Minnesota, and the histopathologic sections were reviewed by Dr. George P. Sayre,* who reported as follows:

"In the cervical spinal cord there is a decrease in the number of neurons in the anterior horns, particularly in the ventrolateral columns.

*Member, section of pathologic anatomy, Mayo Clinic, Rochester, Minnesota.

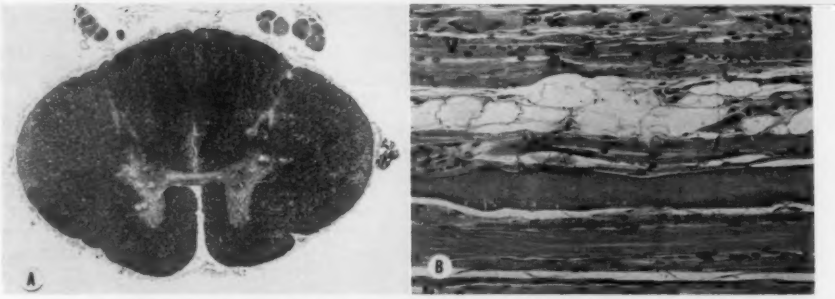

FIG. 17. *A*. Midthoracic spinal cord. There is demyelination of the lateral columns, more marked on the left than on the right, affecting the spinocerebellar tracts and extending into the pyramidal tracts. There is extensive gliosis of the anterior horns. Weigert stain. *B*. Section of muscle. There is marked variability in the size of the fibers; some are swollen with homogeneous cytoplasm; others are atrophic with increased sarcolemmal nuclei; there are occasional masses of cytoplasm with clumps of nuclei. Hematoxylin and eosin stain.

A few cells are pyknotic and a few swollen hyalinized astrocytes are present, particularly in the lateral and ventrolateral horns where frank gliosis is present. The pyramidal and spinocerebellar tracts show a mild disproportion in the size of the myelin sheath; a few phagocytes are present in the myelin sheaths. The Weigert stain shows loss of myelin in the subpial region of the spinocerebellar tracts.

"At the midthoracic level of the spinal cord there is almost total loss of the anterior horn cells and there are only a few cells remaining in lateral horns where swollen astrocytes are present. The myelin sheaths in the lateral columns are swollen and contain cells which have granular lipoid material. In the posterior columns around some thickened vessels, there is slight degeneration of myelin with phagocytosis. The Weigert stain shows demyelination of the spinocerebellar tracts extending into the pyramidal tracts. There is slight demyelination of the interfascicular tracts of the posterior column (figure 17A).

"In the lumbar cord a few anterior horn cells are seen on one side; on the other side only a rare cell remains; there is extensive gliosis with many swollen hyalinized astrocytes within both anterior horns. The anterior roots are fibrosed and only about 20 per cent of the usual number of axis cylinders remain. The lateral columns are small, and a definite decrease in the number of axis cylinders is noted. The posterior columns show a mild fibrosis of blood vessels and a moderate number of lipoid-filled macrophagocytes are present in the myelin sheaths. The Weigert stain confirms the loss of myelin in the lateral columns. In the posterior columns the loss is mainly perivascular.

"In the medulla there is some degeneration of the twelfth nerve nucleus. There is evidence of gliosis.

"The motor cortex is within normal limits; the changes are no different than those in the neighboring cortex.

"Examination of several sections of muscle shows variable degrees of chronic muscle atrophy. One section of a severely involved muscle (figure 17B) shows many thin fibers with long chains of sarcolemmal nuclei; in other fibers the nuclei are found in clumps. Granular atrophy of some fibers, usually in fascicular arrangement, is present. The picture is compatible with chronic muscle degeneration seen in amyotrophic lateral sclerosis.

"Tissues from the pituitary, adrenal, pancreas, and thyroid are essentially normal. The myocardium and kidneys are normal. The lungs show active pneumonia and there are fatty changes in the liver. The testes show a mild decrease in the number of maturated sperm."

The histologic findings of loss of anterior horn cells and degeneration of lateral columns with muscle atrophy are compatible with the accepted criteria of amyotrophic lateral sclerosis. The gliosis in the posterior column and spinocerebellar tracts is somewhat unusual. The degree of gliosis in the anterior horns, although

not usually seen, has been described by others.

The clinical reports of the other members of the family were as follows:

II-3 (father of the propositus) was a 51 year old farmer who was examined at the clinic on May 2, 1910. Ten months previously, the patient had noted muscle twitchings followed by wasting and weakness of the right thigh. The findings reported were as follows: "Right arm, shoulder, pectoral and right leg muscles atrophied. Leg muscles completely paralyzed except sartorius. In upper part are fibrillary twitchings and weakness. Left side twitching in all muscles; more in leg. Some atrophy. Both knee jerks gone. Pupils react to light. Sensation normal. Urine normal. Eye examination, including eye grounds, normal."

Three months later the patient died.

III-6 (brother of the propositus) was a 34 year old unmarried farmer who registered at the clinic on October 19, 1936, with the chief complaint of progressive paralysis of both legs over the past year. Previously, he had been in excellent health. The patient reported the family history as negative; he denied any neurologic disorder in the family.

The patient was unable to walk. Positive findings were limited to the neurologic examination as follows: There was marked muscle weakness with atrophy in the left lower extremity. There was moderate weakness with atrophy in the muscles of the right lower extremity. There were similar weakness and atrophy with fasciculations in the extensor muscles of the neck as well as in the pectoral, shoulder, arm, forearm, and hand muscles. Atrophy and fasciculations were present on the left. The muscle-stretch reflexes were moderately hyperactive in the jaw and upper extremities and absent in the lower extremities. There was no Babinski sign. Sensation was normal and the patient was mentally alert.

The patient died later the same year.

Regarding III-4 (sister of the propositus) the following information was obtained from members of the family. "She had been doing quite poorly for a number of years before she died, but no signs of paralysis occurred until about eight months before she died. A year before her death she had to support herself by selling from house to house, carrying a heavy sample case. About that time she began losing the use of her left arm, which gradually progressed to her left leg, right leg, and right arm. She had been to several clinics where a diagnosis of spinal muscular atrophy was made."

We have recently learned that IV-7, the oldest son of III-4, has developed symptoms of progressive muscular atrophy.

It was difficult to obtain reliable information about the rest of the family, although III-7 was said to be in good health.

The grandfather of the propositus (I-1) was described by his grandson (III-7) as follows: "The obituary of my grandfather .... S., born February 7, 1828, and died at his home on February 5, 1903 (age 75). His last illness was to a large extent without physical suffering. There was a gradual wasting of the physical forces and finally falling into a deep sleep; he breathed his last on Thursday at 2:30 a.m."

No information is available regarding the cause of death of the wife of I-1.

I-1 and I-2 had nine children, seven of whom survived to adulthood. One of these (II-3) is described in earlier paragraphs as clinically having progressive muscular atrophy.

The following information was obtained about his sibling II-9. In 1933, at the age of 63 years, a gradual painless progressive weakness of his right shoulder and hand developed. A few months thereafter, a similar condition began in his other hand and shoulder. There were no remissions. His widow reported that "he could not use either hand or arm; he had to be fed and dressed." His legs, speech, and swallowing were apparently not involved. His local physician diagnosed his illness as a progressive muscular disease. His widow reported that "he lived about eight months." He apparently died of a heart attack unrelated to his neurologic condition.

The information on patient III-9 was obtained from III-1, who wrote that she died of the same disease as Mr. S. (II-3). Very little information was obtained on the mother of III-9. She (II-4) was reported as having died of "nervous prostration" in 1902 at age 40 years.

F Family.—The propositus (II-8 in figure 18) and four of his five children succumbed to progressive muscular atrophy. The father and son were observed at the Mayo Clinic, two of the daughters were patients at the University of Iowa Hospital, and one daughter was observed by Dr. Voris of Chicago and by Dr. Ralph Cloward of Honolulu.

The propositus, a 34 year old mail carrier

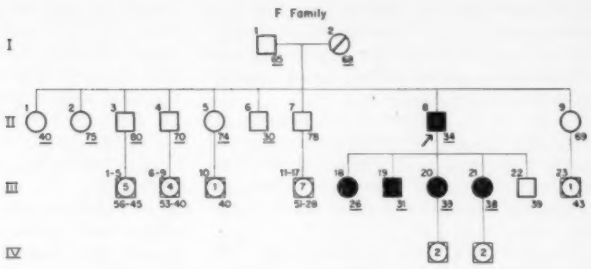

FIG. 18.
Pedigree of F family.

from Iowa, registered at the clinic on February 10, 1915, with the chief complaint of "wasting away of the left arm and difficulty moving the tongue." Past history was noncontributory, and family history was reported as negative. His present illness began about one year before, with wasting and weakness in the left thumb and index finger.

On examination he was found to have flaccid paralysis with atrophy and muscular "fibrillations" in both upper extremities, more marked on the left than on the right. Muscle "fibrillations" were present in the thighs and also in the tongue, which showed marked weakness and atrophy. Muscle-stretch reflexes were absent in the left arm and present in the right arm and legs. The patient died several months later.

The propositus had five children (III-18-22), four of whom have died of progressive muscular atrophy or amyotrophic lateral sclerosis.

The oldest daughter (III-18) developed a progressive neurologic disease at 25 years of age and died at the University of Iowa Hospital 18 months later. Dr. Russell Meyer of the University of Iowa kindly provided an abstract of the record. About March 1933, the patient noted progressive weakness in the lower lip and weakness and wasting of the muscles of the left thumb. Shortly thereafter there was similar involvement of the right thumb. "Fibrillary tremors" were noted in the fingers and hands and later in the arms and shoulders. On October 7, 1933, Dr. Van Epps made a diagnosis of amyotrophic lateral sclerosis. There was steady progression of these symptoms, and the patient was admitted for her terminal illness to the University of Iowa Hospital on July 11, 1934. It was reported that her father had died of a creeping paralysis similar to her own; the family history and past history were otherwise noncontributory.

Examination revealed that there were weakness and wasting which were particularly evident in the flexor and rotator muscles of the neck, the tongue, the lips and the palate, and the muscles of mastication. The hands showed a clawlike deformity bilaterally, with marked atrophy of the thenar and hypothenar eminences and of the interossei. There was marked atrophy of the muscles of the shoulder girdle and arm.

The plantar responses were flexor in type bilaterally. Sensation was normal in all modalities, including the discriminative tests. Congestion of the bases of both lungs developed, and she died on July 17, 1934.

At necropsy, three and a half hours after death, acute inflammatory changes in the respiratory system, skeletal muscle degeneration, and changes in the nervous system were found. There was no evidence of degeneration of the motor tracts in the spinal cord or brain stem; the Betz cells in the prefrontal gyri of the frontal lobes presented a normal appearance. There was marked atrophy of the ganglion cells in the anterior horns of the gray matter of the cervical segments of the spinal cord and to a much less extent the thoracic, lumbar, and sacral segments. There were similar changes in the medulla, involving the twelfth cranial nerve nuclei of origin. Although only slight changes were found in the nucleus ambiguus, the history of dysarthria and dysphagia and the degenerative changes found in sections of the eleventh cranial nerve and the esophageal branches of the tenth cranial nerve indicate that the motor nuclei of origin of the ninth, tenth, and eleventh cranial nerves were involved to some extent. The motor root of the seventh

cranial nerve showed degeneration. The temporalis muscle showed the same type of atrophic changes found in the biceps, trapezius, sternocleidomastoid, gastrocnemius, quadriceps femoris, and tongue muscles.

Patient III-19 (brother of the previous patient) was a 31 year old farmer who registered at the clinic on May 21, 1940, with the chief complaint of progressive painless wasting and weakness of the right arm of six months' duration.

The past history was noncontributory. The patient reported that his father had died at age 33 years of "lateral sclerosis with generalized muscle wasting after a four to five year illness"; that one sister, aged 26 years, had died of "lateral sclerosis with bulbar palsy"; and that three younger siblings were living and well. In November 1939 he had first noticed progressive weakness and muscle atrophy in the right arm and hand. A few months later he noted some difficulty in moving his right leg rapidly. There was no difficulty in eating, swallowing, or speaking.

The positive findings were limited to the neurologic examination. There were moderate weakness, atrophy, and muscle fasciculations over the entire right upper extremity, and a few muscle fasciculations were noted in the left shoulder and leg. Muscle-stretch reflexes were about normal in the upper extremities; the quadriceps femoris reflex was bilaterally hyperactive; the triceps surae were slightly hyperactive. Coordination and the results of sensory examinations were normal.

Laboratory examinations showed normal urine, hemoglobin, erythrocyte and leukocyte counts, and negative flocculation reaction for syphilis. Ther cervical segment of the spinal column was normal on x-ray examination. Cerebrospinal fluid showed 50 mg. protein; otherwise it was negative. The diagnosis was amyotrophic lateral sclerosis. The patient died about nine months later.

Following the death of this sibling, patient III-20 inquired in April 1941 about the prospects that she too might develop this same disorder and what steps might be taken to prevent it. She reported that she was taking large doses of vitamins A, B, C, D, and E as well as wheat-germ oil. A noncommittal reply was made.

In spite of the measures which this patient took, symptoms of progressive weakness and wasting in the left arm developed early in 1948. She was seen by Dr. Harold Voris and others in Chicago in January 1949, and a diagnosis of amyotrophic lateral sclerosis was made. She later went to Honolulu and was seen by Dr. Ralph B. Cloward, from whom the following record-abstract was obtained.

Dr. Cloward examined this patient in June 1949. There was marked weakness of muscles of both the left arm and leg. The left tendon reflexes were slightly hyperactive; Babinski responses were absent. The sensory examination revealed no abnormalities. The diagnosis was amyotrophic lateral sclerosis.

By October of the same year there had been progression, and weakness and atrophy were evident in all four extremities. The right quadriceps femoris stretch reflex was markedly hyperactive. There were still no bulbar signs.

The patient was admitted to Queen's Hospital, Honolulu, on June 4, 1950. Bronchopneumonia developed and the patient died on June 17, 1950. Necropsy, performed about 36 hours after death, showed extensive muscle atrophy, bronchopneumoia, and pleural effusion. Grossly the brain was normal.

Dr. Sayre examined the central nervous system sections and reported that the postmortem changes were so marked that an accurate description or diagnosis was impossible. However, slight but definite degeneration was noted in one pyramidal tract, and there was probably some decrease in the number of anterior horn cells.

While the preceding patient was ill (in 1950) she learned that her younger sister (III-21) had begun to develop a slowly progressive weakness of the right arm. The younger sister was admitted to the University of Iowa Hospital on July 10, 1952. According to her history at that time her illness dated back only nine months, whereas information in her sister's record showed the duration to be about three years. Physical examination revealed wasting of the shoulder girdle with markedly active fasciculations. The thenar and interosseous muscles were moderately atrophic. Flaccidity was noted in the legs. The jaw jerk, knee, and ankle jerks were all hyperactive; Babinski signs were absent. Sensation was intact. The results of laboratory examinations were essentially normal. The diagnosis was amyotrophic lateral sclerosis. About three months later pneu-

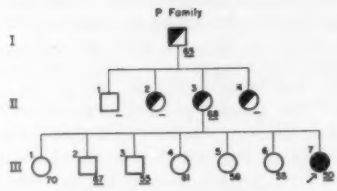

FIG. 19. Pedigree of P family.

monia developed and the patient died. Necropsy was not performed.

The surviving brother (III-22) was living in Hawaii and, on examination by one of us (Kurland) on March 10, 1954, was found to have no neurologic abnormality.

P Family.—The propositus (III-7, figure 19) was a 48 year old Illinois housewife, who registered at the clinic on January 30, 1953, with the chief complaint of a slowly progressive dysarthria of six months' duration. Examination revealed marked signs of bulbar palsy, muscle atrophy in the upper extremity more marked on the left than on the right, and early pseudobulbar and pyramidal tract abnormalities. Coordination and sensation were unaffected. The results of laboratory examinations, including examination of spinal fluid, were normal. The patient died in November 1953, about three and a half years after onset of symptoms.

It was possible to obtain only fragmentary data on this family; but the information available suggested that a neurologic disorder, characterized by bulbar palsy, had been present in three generations (figure 19). In view of the patient's typical amyotrophic lateral sclerosis and her reference to her mother's disorder, which was said to be similar to her own, as "creeping paralysis" or "bulbar palsy," it is quite possible that "bulbar palsy" as used by this family would refer to amyotrophic lateral sclerosis with bulbar signs.

The propositus was the youngest of seven children. The oldest sibling (III-1), aged 70 years, was living. She was said to be "stiff and feeble." Sibling III-2 had died of a "stroke" at age 67 years; sibling III-3 had died of a renal ailment at age 55 years; the next three siblings were said to be living and in fair health.

The father of the propositus was said to have died of a cerebral hemorrhage at the age of 45 years.

The mother of the propositus (II-3) died of "creeping paralysis" or "bulbar palsy" at the age of 68 years. Two of her sisters (II-2 and II-4) also died of "bulbar palsy," but the ages at death and other medical information were not available. A brother (II-1) had died of "heart disease." The maternal grandfather of the propositus (I-1) was also said to have died of "bulbar palsy" at the age of 65 years.

CA Family.—The propositus, a 46 year old housewife from Tulsa, Oklahoma, registered at the clinic on February 24, 1954. In May 1953 she had begun to notice muscle "cramping" in the legs and progressive weakness in the lower extremities. On examination, she was found to have slight weakness with fasciculations and possible muscle atrophy in the upper extremities and moderate weakness and atrophy in the muscles of the lower extremities. Knee jerks, however, were slightly hyperactive; Babinski sign was absent. Sensation was normal.

The patient's mother had died at age 45 years, after a progressive wasting of muscles and "creeping paralysis" which reportedly had lasted nine years. The mother had two siblings, one of whom died at age 55 years of heart disease; the other was alive at age 80 years. It was not feasible to obtain additional information on this family.

B Family.—There are four cases in this family: the father and three of his seven children. Three siblings (two brothers and a sister) succumbed to a rapidly progressive form of amyotrophic lateral sclerosis (figure 20). The details of the

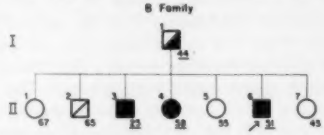

FIG. 20. Pedigree of B family.

illness in the father (I-1) are not available, although he is said to have died at age 44 years of a progressive paralysis of the same type that affected his three children.

The history reveals the onset of progressive painless weakness and muscle

atrophy beginning in the left upper extremity in two (II-3 and II-4) and in the left lower extremity in the other (II-6). In each of the three siblings there was rapid and unrelenting progression with involvement eventually of the musculature of all four extremities. Death ensued eight or nine months later because of respiratory paralysis due to involvement of the cervical and bulbar nuclei. In all three, the weakness and atrophy were preceded by generalized muscle fasciculations.

The propositus, aged 50 years (II-6), registered at the clinic on March 26, 1951, with a history of progressive painless weakness with atrophy and muscle twitchings, which had begun in the left lower extremity six months earlier but which soon involved all four extremities. The family history disclosed that his father had died of a "creeping paralysis" similar to that to which an older brother had succumbed. The brother had been observed at the clinic 23 years earlier.

The general physical examination, blood counts, serologic data, sedimentation rate, and urine studies were negative. Neurologic examination disclosed fasciculations of the tongue, bilateral intrinsic hand muscle atrophy and weakness, worse on the left than on the right, and weakness and atrophy throughout both lower extremities, again worse on the left than on the right. Muscle-stretch reflexes were hyperactive in the upper extremities, normal in the right lower, and absent in the left lower extremities. Hoffmann's sign was present bilaterally; there was no Babinski sign. All modalities of sensation were intact. The cranial and cervical spinal x-rays were normal. The cerebrospinal fluid dynamics were normal: the protein was 160 mg. per 100 cc.; there were no cells; Kolmer reaction and gold curve were negative. The electromyographic changes were considered "compatible with a diagnosis of amyotrophic lateral sclerosis." Although the diagnosis of neuronitis was considered in view of the spinal fluid protein, the diagnosis of amyotrophic lateral sclerosis was considered most likely at time of dismissal from the hospital. The patient's course was progressive and he died of bulbar paralysis three months later (nine months after onset).

The patient's brother (II-3), a 25 year old male filling-station attendant, had registered at the clinic on May 28, 1928, with the chief complaint of progressive weakness and atrophy which had begun in the left thumb and forearm. The general physical examination was noncontributory. Muscle fasciculations were noted in all four extremities. Weakness was marked on the left side of the face and the extremities, particularly distally, and early weakness and atrophy of the intrinsic muscles of the right hand were also noted. The muscle-stretch reflexes were more active on the right side than on the left but were somewhat hyperactive in all four extremities. The abdominal reflexes were present; no pathologic reflexes were noted. In addition, there was slight horizontal nystagmus on gaze to the right. Sensation and coordination were normal. Kolmer reaction on the cerebrospinal fluid was negative; 1 lymphocyte per cubic millimeter was found.

The diagnosis of amyotrophic lateral sclerosis was considered, but because of the fairly rapid course of the disease, the diagnosis of a chronic anterior poliomyelitis was made. The patient became progressively worse and succumbed about nine months after the onset of his muscle weakness.

Dr. Roland P. Mackay of Chicago and Dr. Lewis Woodruff of Joliet, Illinois, provided the history on II-4, a 58 year old housewife who died of bulbar paralysis about eight months after onset of weakness, atrophy, and muscle twitchings in the left hand in September 1951. Before she developed progressive dysphagia and respiratory paralysis, muscle atrophy and weakness were seen to involve the upper extremities and the tongue. Early in the course of her illness muscle-stretch reflexes were brisk and equal on the two sides. Plantar responses were normal, except for an occasional questionable Chaddock's sign on the left. All sensory functions were normal. The cerebrospinal fluid was negative, with protein of 34 mg. per 100 cc., normal cell count and gold curve, and a negative Wassermann reaction.

Recently we learned that II-2 had begun to notice weakness of his hands but we were unable to obtain any additional information.

EXAMINATION OF 58 CASE RECORDS

The foregoing data strongly suggest that the familial aggregation of cases of

amyotrophic lateral sclerosis is not as rare as most authorities have reported. However, since the instances described here were highly selected, that is, they were specifically recalled by members of the section of neurology of the Mayo Clinic because of family history, it seemed desirable to determine the ratio of "positive" to "negative" family histories in a consecutive series of cases.

Ideally, to assure completeness, family histories should be obtained by persons acquainted with the disorder being studied and experienced in methods of collecting genetic data. Preferably, newly registered patients and their families should be interviewed; but since it would have taken many months to develop a large series of pedigrees, we resorted to a retrospective case study first. We examined the records of all Minnesota patients who registered at the Mayo Clinic from 1945 to 1953 inclusive whose diagnosis was amyotrophic lateral sclerosis. Fifty-eight records in which the clinical description was that of typical amyotrophic lateral sclerosis were analyzed.

We found that the routine family history which is obtained, particularly when the disease suspected is presumably not hereditary, is usually fragmentary and is rarely complete for genetic studies. Data on the state of health or age and cause of death are usually recorded for the parents and siblings only, in some cases parents have died of unknown causes during the patient's childhood, often parents or siblings have died of other causes before passing through the age of risk for amyotrophic lateral sclerosis, and unless the patient volunteers information on other family members there is not likely to be any other history recorded. As was noted previously, patients often withhold or do not know pertinent family history. When dealing with a disorder as rare as amyotrophic lateral sclerosis and with a clinical name so difficult for the average layman to repeat, much less remember decades after such a death in the family, we would rarely expect the patient to know the disorder by its full medical name; more commonly the term "creeping paralysis" or "chronic polio," used to describe a slowly progressive disorder in an adult of middle or advanced age, would have to be accepted as presumptive evidence of the same disorder in the family. When such a death was reported in one of the patient's offspring, parents, grandparents, siblings, or parents' siblings, the family history was considered "positive."

In the 58 records studied, there were five positive family histories. In one other record, there was a comment that a hereditary neurologic disorder in the paternal grandfather was an etiologic factor. (No other information was recorded for other members of the family.) In another record the cause and age at death for the parents were listed as unknown, but the neurologist recorded as a questionable etiologic factor the matter of hereditary neurologic disease.

The five "positive" histories were as follows:

1. A 55 year old housewife of Swedish descent reported that her mother had died at age 72 years of what she thought was "amyotrophic lateral sclerosis."

2. A 44 year old machinist of Swedish descent reported that one uncle had had a neurologic disease characterized by wasting of arm and leg muscles similar to his own.

3. A 51 year old housewife of German descent reported that her mother died of "creeping paralysis" which began in the hands.

4. A 46 year old farmer of English descent reported that the age and cause of death of his mother were unknown. His mother's brother

died of "creeping paralysis." Two of his brothers, he thought, had died of "spinal meningitis." No other details were reported.

5. A 50 year old farmer had amyotrophic lateral sclerosis and Pick's disease. His wife reported that the patient's father had died of "creeping paralysis."

It was not feasible to carry on any follow-up in these cases to determine the validity of either the "negative" or the "positive" family histories or to determine the true incidence of cases in the latter families. However, the data are presented because of the general impression they convey that positive family histories are at times encountered in a review of clinical records, and these in conjunction with the detailed pedigrees that we have presented are additional evidence of the importance of heredity in amyotrophic lateral sclerosis. To overcome some of the difficulties mentioned in reviewing these histories, we are carefully studying the family histories of a large series of new patients who have amyotrophic lateral sclerosis.

COMMENT

Ninety cases of amyotrophic lateral sclerosis, progressive muscular atrophy, or progressive bulbar palsy, occurring in 18 families (not including the Guam experience), have been reviewed and six new pedigrees with 34 affected individuals have been reported here. In addition, a review of 58 clinical histories of patients who had amyotrophic lateral sclerosis revealed at least five instances in which the family history was presumably "positive" for other cases.

The clinical disorder which was described in detail in our familial cases cannot be distinguished from that of the classic form of amyotrophic lateral sclerosis. No "juvenile" form was observed in these families. Neither the "rudimentary" form of the illness as described by Dawidenkow[11,12] nor the "arrested" form described by Swank and Putnam[10] was noted. Clinical pictures consistent with the diagnosis of progressive muscular atrophy, progressive bulbar palsy, or amyotrophic lateral sclerosis in members of the same family were found; no patient with external ophthalmoplegia was observed and intellectual defect was reported in only one case. The symptoms of progressive muscular atrophy were found to occur before and predominate over the symptoms of corticospinal or corticobulbar tract involvement. Upper motor neuron signs, if they occurred, were usually seen late in the course of the disease, and where bulbar involvement was early, the patient frequently succumbed before upper motor neuron signs became evident. Clinical signs of pyramidal tract involvement were often observed in many patients, and pathologic degeneration in the lateral columns was noted in two of the three cases in which pathologic specimens were available.

Except for the B family, the clinical picture in members of the same family in our series varied quite a bit from the standpoint of age of onset, earliest symptoms, and clinical course; there was no similarity in type of onset such as Robinson[41] had described in the four members of his family, whose first symptoms were noted in the right upper extremity.

The variability in the clinical course of the disease is noted, for example, in the F family. One sister developed progressive signs of lower motor neuron involvement only and these were almost limited to the bulb and cervical segments; her sister had the typical picture of amyotrophic lateral sclerosis with bulbar signs. Postmortem findings in the

two sisters were consistent with the diagnosis of progressive spinal and bulbar muscular atrophy and amyotrophic lateral sclerosis, respectively. Such findings support the hypothesis that progressive muscular atrophy is part of the total picture of amyotrophic lateral sclerosis.

In the patient in the S family on whom necropsy was performed, there was slight posterior column demyelination in the spinal cord although no sensory abnormalities had been observed at the clinical examination. The spinal cord also showed anterior horn cell degeneration and demyelination in the lateral columns. Posterior column demyelination in amyotrophic lateral sclerosis has been reported before. Hassin[50] described one patient with such changes in the cord which he considered as "amyotrophic lateral sclerosis complicated by subacute combined degeneration." However, several of the discussers of Hassin's paper pointed out that the posterior column changes were not necessarily a coincidental complication but might at times be part of the picture of amyotrophic lateral sclerosis. Schaller stated that "amyotrophic lateral sclerosis is often associated with degeneration of the posterior column of the cervical region . . . this was brought out at the symposium during the Charcot Centenary . . . and I have seen such cases."[50] Among the 53 patients having amyotrophic lateral sclerosis in whom postmortem findings were studied by Lawyer and Netsky,[51] one had "demyelination of the fasciculus gracilis in the cervical and thoracic sections of the spinal cord with well-defined gliosis." The authors felt that this was a coincidental finding or a complication of the disorder rather than an unusual variant of amyotrophic lateral sclerosis. Biemond[52] has described three cases of "chronic anterior poliomyelitis" (the clinical description is consistent with progressive muscular atrophy) in which varying degrees of demyelination of the posterior columns but not of the lateral columns were noted. The possible significance of posterior column degeneration in relation to amyotrophic lateral sclerosis will be considered at another time.

In 1926 when the consensus was that amyotrophic lateral sclerosis was not hereditary, Schaffer[53] and Lehoczky and Schaffer[54] (and later von Sántha)[55] suggested a hereditary basis for the disease on the following grounds: 1) The central nervous system involvement was predominantly "a motor system disease . . . with a segmental distribution." 2) "The pathologic process proceeds as an elective degeneration of the neuroectodermal elements without any diffuse spread or any involvement of inflammatory mesodermal components." 3) "Such an abiotrophic process is more indicative of an ectodermal genetic illness than of one due to noxious agents."[55]

Wilson,[1] whose viewpoint that amyotrophic lateral sclerosis is not hereditary has remained generally accepted among neurologists, has argued in favor of a toxic origin and stated that Schaffer and Lehoczky tended to "exaggerate the evidential value (of heredofamilial examples of amyotrophic lateral sclerosis)." Wilson stated that "too much significance has been attached to familial types which are far outnumbered by individual adult cases; and doubt exists whether they always belong to the same group as the latter."

Our report would seem to provide considerable evidence that typical amyotrophic lateral sclerosis in familial aggregations is not as rare as was formerly

believed and that such cases when they do occur cannot be distinguished clinically or pathologically from the "sporadic" cases.

Although some unknown external factor might be of etiologic importance in amyotrophic lateral sclerosis, the pathologic characteristics of the disorder and the data presented here do not support such a hypothesis where familial aggregation is noted. The high family incidence is not limited to a brief period of time when various members might be exposed to a common agent but is spread over generations in time. Furthermore, it was frequently noted that the disease continues to occur in family members living in different environments which, at the same time, might not be different from that of their contemporary unaffected neighbors. Although we have only few data at the present time, we have not found that change of environment influences the outcome of the disease.

Each of the new pedigrees presented here is compatible with a mendelian dominant form of inheritance. Although recessive inheritance must be considered, the extremely low probability of observing this disorder in successive generations so consistently makes this form of inheritance unlikely. In nearly all instances in which data were available, an affected individual had one affected parent. The exceptions are noteworthy. In the C family (figure 15A) III-4, who was examined by one of us (Kurland), appeared to be free of any neurologic disorder; yet she apparently transmitted the trait to her son (IV-7) who died of amyotrophic lateral sclerosis; her father (II-1), who did not have amyotrophic lateral sclerosis, apparently inherited the trait from his mother (I-1) and transmitted the trait to three of his five other daughters (III-1, III-3, and III-5), in whom the disease developed. Neither of these individuals (II-1 or III-4) survived to the full age span of risk from this disorder, since cases are known to begin in the seventies and later; however, the possibility that the condition known among geneticists as "incomplete penetrance"* may have applied here, must also be mentioned.

In those instances in which all siblings in a more recent generation were free of the disorder, the parent was also free of the disease. (For example, again in the C family, note the absence of the trait in the offspring of II-4, II-6, and II-8.)

Our large collection of pedigrees enables us to study by statistical methods several items of interest:

The average age at death for the entire series is 47.4 years (table 1) which corresponds with our experience on Guam, where the average age at death was about 47 years and the mean duration from onset to death three years.

The duration of illness in the cases in our series is not amenable to careful analysis, since the majority of patients included had died many years before and the informants usually gave only an approximate duration. There appeared to be a tendency on the part of some family members to describe all cases as being of about the same duration, although in the B family this was verified by the clinical records. Duration was

*"Penetrance," as used here, refers to the percentage of individuals who, when they possess the gene, show any effect from it. Theoretically, if penetrance is complete and the gene is dominant, half of the offspring of an affected heterozygous individual will develop the trait. When an individual can transmit the gene responsible for the trait, yet shows no obvious manifestation of the disorder, it is said that the penetrance of the gene is incomplete.

probably more often underestimated than overestimated by the family or even occasionally by the patients, since they tended to date the onset to a more recent severe or obvious difficulty, as has also been noted in other studies of chronic neurologic disease.[56] The longest duration in our series was that of III-21 of the F family, which we know was at least three and a half years, although the patient reported it as nine months' duration on her hospital admission shortly before she died. The longest duration reported in the collected series was seven years for II-6 of the Wetherbee (Massachusetts) family. Most of the patients in our own series and those of the other pedigrees collected, regardless of whether they were characterized by progressive muscular atrophy or the full amyotrophic lateral sclerosis picture, reported durations of only about two years. Although this is slightly less than that reported in the Guam experience[9] and other series of cases of amyotrophic lateral sclerosis,[57] Müller[27] reported much longer duration in those cases which had no pyramidal tract findings.

The age at onset is not given specifically in many cases in the collected series, although age at death and some indication of the rapidity of the disease process is frequently reported.

If we assume that average duration of onset is about two years when it is not specifically stated, we have some indication of average age at onset of the disease in most of the families reported. There was great variability in the age at onset of the illness in different families, the significance of which is unknown. In some, for example the family reported by Montanaro and Lopez[43] and our own F family, the onset was noted in all cases at a relatively early age, whereas in the families reported by Lovell,[44] by Robertson,[13] and the second family reported by Barraquer-Ferré and Barraquer-Bordas,[22] the age at onset was quite late in life. In the other families for which there are age-at-onset data, there was a marked variability among family members, with the average about 47 years and the range from the late twenties to the early sixties. The variability in age at onset is well illustrated in the large collection of cases in our own C family, where the onset varied from 27 years in II-2, to 62 years in her sister, II-7. Most patients in those families with a large number of affected persons noted onset of symptoms about the fifth or sixth decade.

We have attempted to compare the incidence in the two sexes. On Guam and in numerous other countries for which statistics are available, amyotrophic lateral sclerosis is one and a half to two times as frequent in males as in females. This is "presumably due to a higher penetrance of the disease in males."[9] In the series of reported pedigrees (upper half of the table), there were 53 affected males and 37 affected females. (The ratio is 1.4 males to 1 female.) However, in our own pedigrees, there is a preponderance of affected females (20 females to 14 males). Since this type of comparison does not take into consideration the ratio of all males to females in the families, we compared the sex ratios for the "unaffected" as well. However, to limit this comparison to the groups in which the disease might occur in either sex, this was done only for sibships in which at least one individual was affected and in which there was reasonably complete information on the entire sibship. This was done for the reported collection of pedi-

TABLE 1

SELECTED CHARACTERISTICS OF PATIENTS HAVING HEREDITARY AMYOTROPHIC LATERAL SCLEROSIS AND PROGRESSIVE MUSCULAR ATROPHY

Source	Race or nationality and residence of patients	Number affected			Average age at death of patients, years	Complete sibships (see text)					
						Affected			Unaffected		
		T	M	F		T	M	F	T	M	F
Aran*[33]	French, France	4	3	1	..	..	..	..	..	..	..
Osler[34] and Brown[35]	U. S. (Vermont)	17	11	6	45	16	10	6	8	4	4
Hammond[36] and Brown[35]	English, U.S.(Mass.)	9	6	3	..	8	5	3	13	8	5
Bernhardt[38]	German, Germany	4	3	1	40	4	3	1	7	3	4
Bruining[39]	German, Germany	2	2	0	..	..	..	..	..	..	..
Gowers*[27]	English?	..	..	..	..	..	..	..	..	..	..
Dana[40]	"Old American"—U.S. (N. Y.)	10	4	6	44	8	3	5	4	1	3
Robinson*[41]	U.S. (Midwest)	4	3	1	48	..	..	..	..	..	..
Hamilton[42]	U.S. (Wisconsin)	4	1	3	42	2	0	2	4	3	1
Montanaro and Lopez[43]	Spanish, Argentina	4	4	0	28	3	3	0	0	0	0
Lovell[44]	U.S. (Michigan)	4	2	2	63	4	2	2	6	2	4
Dittel[45]	German, Germany	8	4	4	47	6	2	4	7	2	5
Schroeder*[46]	Spanish, Uruguay	3	0	3	..	..	..	..	..	..	..
Barraquer-Ferre and Barraquer-Bordas (family 1)[32]	Spanish, Spain	3	1	2	48	2	0	2	1	0	1
Barraquer-Ferre and Barraquer-Bordas (family 2)[32]	Spanish, Spain	2	2	0	60	1	1	0	0	0	0
de la Vigne and Ahmad*[47]	French?, North African?	2	2	0	..	..	..	..	..	..	..
Robertson[12]	Scottish	4	2	2	66	3	1	2	2	2	0
Dewey[48]	U.S.	2	1	1	50	2	1	1	7	3	4
Rose*[49]	U.S. (Mass.)	4	2	2	..	..	..	..	..	..	..
Koerner*[4]	Chamorro, Guam	..	..	..	..	..	..	..	..	..	..
Subtotal		90	53	37	47.1†	59	31	28	59	28	31
Kurland and Mulder C family	English-Irish (Iowa)	12	4	8	48	11	4	7	10	6	4
S family	English-German (South Dakota)	6	4	2	51	6	4	2	7	3	4
F family	Irish (Iowa)	5	2	3	34	5	2	3	8	4	4
P family	Scottish (Illinois)	5	1	4	61	4	0	4	3	1	2
CA family*	English? (Oklahoma)	2	0	2	..	..	..	..	..	..	..
B family	German (Illinois)	4	3	1	45	3	2	1	4	1	3
Subtotal		34	14	20	48.0†	29	12	17	32	15	17
Total		124	67	57	47.4†	88	43	45	91	43	48

*Insufficient data.
†Weighted average.

grees as well as for our own pedigrees (table 1). An individual was considered "unaffected" if he remained free of the disease and had attained the average age of all those who had died of amyotrophic lateral sclerosis in his particular family.

In the sibships studied in the reported collection of pedigrees, there were 31 affected males and 28 affected females;

there were 28 unaffected males and 31 unaffected females. In this group at least there is no clear indication of a difference in the incidence rate by sex. In our own series there were 12 affected males and 17 affected females, 15 unaffected males and 17 unaffected females. This comparison does not reveal a selectivity for males as has been reported in many series of "sporadic" cases, the mortality statistics for several countries, and our own experience on Guam.[9] The possible explanations for this discrepancy will be reviewed at a later date.

If we now compare the total number of affected and unaffected in these same sibships, we find 59 affected and 59 unaffected in the reported series and 29 affected and 32 unaffected in our own pedigrees. These findings suggest that in the sibships studied, about 50 per cent of the siblings developed the disorder. If we allow for the possible bias of excluding those sibships in which no case occurred but in which the trait may still have been present, the percentage of affected in the sibships would be somewhat less than 50 per cent. We have already noted in II-1 and III-4 of the C family (figure 15A) as well as in II-2 of Dana's family (figure 5) and II-2 of Robertson's family (figure 13) examples of persons who themselves were not affected but apparently transmitted the trait to their offspring.

The pedigrees presented here indicate that amyotrophic lateral sclerosis does occur in familial aggregations, presumably as a dominant hereditary trait. The large number of affected persons in these pedigrees contrasts markedly with the large series of negative family histories of Wechsler and associates,[5] Curtius and Pass,[28] Dawidenkow,[11] Müller,[27] and Van Bogaert.[26] In our review of 58 cases the family history was highly suspect in only five cases, or about 9 per cent. Even in our own recent experience in the series of cases we are developing where we have attempted to obtain detailed family histories from the patient, negative family histories are still found in the large majority of the cases.

This raises the question of whether the majority of apparent "sporadic" cases are related to the "familial" cases.

We have already pointed out how often patients either do not know or do not care to disclose pertinent family history, so that our finding of about 9 per cent of positive family histories in a consecutive series of cases may actually be lower than correct. On the other hand, the striking collection of pedigrees reported here which might suggest that all cases are of familial origin might also be incorrect, for there is a tendency among investigators to report or recall, not the average or usual pedigree, but only the more striking pedigrees and these cases may be the ones which actually have a very low probability of occurrence. We are still faced with the fact that the majority of family histories are negative. Although some of these sporadic cases may represent new mutations, it is also conceivable that the clinical syndrome of amyotrophic lateral sclerosis may be due to some nonhereditary cause as well as to a genetic factor responsible for the cases described here. It remains to be seen whether the "sporadic" cases have a different etiology than the "familial" cases.

In the F family (figure 18), in generation II, one sibling, the propositus, developed the disorder. His mother was said to have had some difficulty in walking and possibly some difficulty with her bladder in the last few years of her

life, but we are unable to determine whether she had a condition related to amyotrophic lateral sclerosis or not. If the mother did have some form of hereditary amyotrophic lateral sclerosis, it is of interest that only one of her nine children developed symptoms. Of course, this could be a chance ocurrence and the propositus might have been the only one to carry the trait. The other possibility is that some of his siblings carried the trait but did not show any effect from it; a third possibility is that the mother did not have the disease and, in fact, did not transmit the abnormal gene. This raises the possibility that the illness in the propositus represents a genetic mutation, which could then be inherited by half his offspring. Such spontaneous mutations are known to occur in other hereditary disorders, such as retinoblastoma, neurofibromatosis, and achondroplasia.[58,59]

Amyotrophic lateral sclerosis apparently occurs in all races.[9,60,61] The families in our own pedigrees and case reports are predominantly of English, Irish, German, or Scandinavian descent; but since persons of such national origin constitute a very large segment of the patients seen at the Mayo Clinic, no conclusions can be drawn from these data.

In the review of the literature earlier in this paper, four of the pedigrees cited were in families of Spanish descent, the others occurring among various European nationalities and among families of uncertain national origin in the United States. The significance of the Spanish cases in relation to the Guam experience will be considered at a later date.

SUMMARY AND CONCLUSIONS

The amyotrophic lateral sclerosis symptom complex, which includes progressive muscular atrophy and progressive bulbar palsy, has been defined and the criteria for this diagnosis have been described. Most authorities who have written about the subject in recent decades indicate that the disorder is nonfamilial and not hereditary. Our review of the literature of the last 100 years revealed that in the latter part of the nineteenth century many neurologists considered these disorders as hereditary but that in recent decades the opposite viewpoint has prevailed. Throughout the period from 1850 to the present, at least 18 extensive pedigrees involving 90 individuals with progressive muscular atrophy, progressive bulbar palsy, or amyotrophic lateral sclerosis have been reported. Clinically and pathologically the cases described are acceptable as the amyotrophic lateral sclerosis symptom complex. We have added six pedigrees with 34 affected individuals to this collection from recent Mayo Clinic observations. The clinical characteristics of the patients whom we observed and the pathologic findings in three of our cases are described. Two of the latter were sisters; anterior horn cell degeneration was present in the spinal cords of both, but only in one was there lateral column demyelination. In the third case, anterior horn cell degeneration was present but the demyelination was somewhat more diffuse than is usually seen.

The familial aggregations in almost all pedigrees are compatible with a dominant form of inheritance, although occasionally an individual who had apparently inherited and transmitted the gene remained free of the trait. The age at onset, the duration of the disease, and the selectivity by sex and nationality are discussed. In a preliminary study of case

histories of amyotrophic lateral sclerosis at the Mayo Clinic, evidence of additional cases in the family was found in five of 58 reports reviewed.

It is our impression that amyotrophic lateral sclerosis does occur as a hereditary disease and that such a basis may account for a significant proportion of all cases. Whether the etiology of the sporadic cases, which remain in the majority, differs from those which are on a hereditary basis remains to be seen.

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CORRECTION: In the first section of this paper, on pages 190 and 191 of the March 1955 issue of NEUROLOGY, figures 4 and 5 were transposed and should be reversed.

Effect of Combined Afferent Lesions on Motor Function

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OF THE RESEARCH which has been performed on the afferent system for the purpose of studying motor deficits, it appears that the dorsal roots of the peripheral nerves, the posterior columns of the spinal cord, and the parietal cortex of the cerebral hemisphere have been chosen and experimented upon singly. The monkey has been the favored experimental animal. As far as is known, no combination lesions involving these portions have been attempted. Nor have the physiologic results obtained following single lesions in the monkey been critically compared, with the exception of the dorsal roots versus the posterior columns.[1] In the latter investigation, a wide disparity was found between the effects of dorsal rhizotomy and section of the posterior columns. Destruction of the pathway in the posterior funiculus, which is thought to be concerned principally with the conduction of sensations from the muscles, tendons, and joints, produced relatively minor defects in muscular physiology. Two possibilities in interpretation were suggested. Either other ascending, muscular afferent tracts than those located in the posterior columns exist or cutaneous and possibly visceral afferents may play a significant role in motor function. The former contingency has been suggested by Gardner and Haddad.[2]

Because of the belief that the afferent system as a whole may possibly be vital in carrying the impulses which initiate, direct, and control voluntary movements, it was considered to be of value to note the short and long range effect of combined lesions on it in the monkey.

MATERIAL AND METHODS

A total of 16 monkeys (Macacus mulatta), weighing between ten and 12 pounds, were operated upon surgically. In seven, combination lesions were made in the left dorsal roots from cervical two to thoracic four inclusive, plus removal of the right parietal cortex. The left dorsal roots and left parietal cortex were operated upon in one. The right dorsal roots and the left parietal cortex were treated in the same way in two animals; in two more, section of the posterior columns at cervical one was added. The

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right dorsal roots to the upper extremity plus cutting of the dorsal columns at the level of cervical one was also performed in three monkeys. Finally, the left dorsal roots, the left parietal cortex, and the posterior columns at the level of cervical one were sectioned in one animal. A pair of iridectomy scissors were employed to sever the dorsal roots, a small, sharp-pointed scalpel served to incise the posterior funiculus, and the suction technic was used for removal of the parietal cortex.

In all of the animals, the second operation was made usually within a week, or close to this time interval, following the first operation. From this series, it was possible to determine what effect two or three lesions, involving well-known parts of the afferent system, would have on phasic and tonic muscular activity in an upper extremity.

Fourteen of the 16 monkeys were studied for postoperative intervals from about two to 13 months. Two were sacrificed before the second month. They were generally observed while in their cages postoperatively, and they were studied more specifically by means of neurologic examination while strapped to a specially devised monkey chair.

The results of the findings in the animals with the combination lesions of the afferent system have been compared critically with those reported previously on the dorsal roots,[3,4] on the posterior funiculi,[1] and with a series of unilateral parietal cortex ablations in 11 monkeys (unpublished).

The central nervous systems of the animals were studied grossly and histologically to check the extent and nature of the lesions. Silver nitrate and protargol stains were employed for the latter.

RESULTS

It is judged that combination lesions of the afferent system in the monkey, which involve the parts of the dorsal roots and parietal cortex concerned with the innervation of one upper extremity, produce a severe and flaccid type of paralysis which is unaccompanied by any overt signs of restitution of function over a one year postoperative interval.

These dual injuries affect such primitive functions as postural support, grasping, and climbing, as well as the more refined hand and digital movements. An upper extremity becomes of little or no physiologic value to the animal. It is pendulous and swings helplessly when manipulated during examination. There is no checking reaction present, indicated by the fact that the arm falls as a dead weight when released from an elevated position. If the normal extremity is tied, the animal is unable to use the affected member effectively for any type of movement. No matter how hungry the animal may be, eating is performed dog fashion. A slight amount of resistance to passive movement may be exhibited at the shoulder and occasionally at the elbow, but there is little or no evidence of it in the wrist and finger joints. The biceps and grasp reflexes are both absent. The deficit in respect to movement is judged to be near maximal. If the parietal cortex operation follows section of the dorsal roots, there is no added motor loss produced; if it precedes it, the dorsal root section increases both the existing atonia and the paralysis.

Section of the posterior columns, superimposed on the parietal cortex and dorsal rhizotomy operations, does not enhance or decrease the degree of tone or paralysis.

When the chronic effects of a dorsal rhizotomy versus removal of the left parietal cortex which affects the contralateral side are compared, the former produces much the more serious deficits. In a monkey with such a pair of lesions, the parietal extremity recovers within a three month postoperative period so that it can be used for postural support, grasping, general phasic movements, and limited eating with the fingers. The main defect which remains is some dysmetria and incoordination. Although subnormal, the tone and resistance to passive movement are greater on the parietal side but they approach normal as the postoperative period is prolonged. None of these is true in the upper extremity which has all the dorsal roots sectioned. It remains flaccid, atonic, almost completely paralyzed, with no accompanying signs of restitution.

On comparison of the results of the operations on the afferent system in the present experiment and others,[1,3,4] the paralytic factor is rated as follows:

1. Complete dorsal rhizotomy of a brachial plexus causes near maximal flaccid paralysis which endures with little or no signs of restitution of function. All aspects of motion are involved, tone, posture, and phasic movements.

2. Ablation of parietal cortex results in a less severe type of paralysis, which has a reduced effect on posture, tone, and phasic movements. Full, or near full, restitution of function is possible within three months postoperatively.

3. Section of the posterior columns produces the least motor deficits and these are temporary. There is no true paralysis and the appendages can be used for postural support, sitting, standing, walking, running, and eating from the time of the operation.

The histologic examinations which were made to determine the placement and extent of the lesions in the dorsal roots, the posterior columns, and the parietal cortex showed no equivocal findings.

COMMENT

On the basis of experiments which have been performed to date on three separate divisions in the monkey, both singly and in combination, it appears that the afferent system may be highly important in the over-all function of voluntary motion. When the dorsal roots, the fasciculi gracilis and cuneatus, and the parietal cortex are all destroyed in one animal by surgical lesions, severe motor deficits result from which there are no signs of recovery. The paralysis is much greater and more enduring than that resulting from total destruction of the motor cortex (area 4 of Brodmann). From the physiologic viewpoint, these afferent parts collectively seem to be more important than the so-called motor region in the cerebral cortex.

When evaluating the three afferent systems according to their physiologic importance in motor function, the dorsal root system is ranked first, the parietal cortex second, and the fasciculi gracilis and cuneatus a poor third. Impulses coursing over the dorsal roots related to an extremity are a necessity in carrying out any kind of purposeful movement. It seems to be true that a safety factor exists in the root system so that a certain percentage of the fibers or one root alone, such as cervical seven, can carry on normal function in the upper extremity,[3,4] but an animal like the monkey cannot satisfactorily adjust to the loss of them all. Initiation of useful movements and restitution of

function for at least a year are also lost in dorsal rhizotomy. By contrast monkeys can recover completely within a period of three months after parietal cortex ablations and after section of the posterior columns.

A disputed question in the field of experimental and clinical neurology is whether lesions of the pyramidal tract cause flaccidity or spasticity. One school leans toward the former, a second to the latter. What the criteria have been for evaluating spasticity and flaccidity is difficult to state. It is the author's opinion, based on the results of studying the effects of dorsal rhizotomy, section of the posterior funiculi, and ablations of the parietal and motor cortices in the monkey, that true, or near true, flaccid paralysis results only when all the roots to an extremity are cut. There is considerable difference in the tonal quality in central cortical operations, whether the lesions are made in front or behind the central sulcus. When compared with the root sections, more tone and more resistance to passive movement are present following the cerebral operations. There is also more checking reaction, more postural, supportive ability, and eventually more chance of recovery.

The variations outlined in the preceding paragraph may mean that different neurologic factors are operating in each system. It is natural to think that the muscle afferents are important. In this connection Gardner and Haddad[2] have obtained results suggesting that muscular afferents may course up to higher cerebral centers via the lateral as well as the posterior column.

CONCLUSIONS

Combined lesions involving the dorsal roots, the dorsal columns, and the parietal cortex in the monkey produce serious and relatively long-lasting deficits affecting all aspects of motion, tonic, postural, and phasic. No restitution of function is possible within one year. Single lesions of these three systems cause widely divergent results, both in the degree and the quality of paralysis. The divisions, ranked according to severity of motor loss and tone, are as follows: dorsal roots, parietal cortex, posterior columns. The first is near maximal and the last is near minimal. The flaccidity which occurs when all the dorsal roots are severed to an extremity offers a standard for pure or near pure flaccidity; it is believed that no cortical operation, whether of the motor or sensory cortex, matches the dorsal root atonia either from the acute or chronic viewpoints. Different neurologic factors or influences affecting motor physiology seem to operate in the dorsal root, the posterior column, and the parietal cortex systems.

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Kemadrin in the Treatment of Parkinsonism

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THE INCOMPLETE and often unsatisfactory benefit of the natural belladonna alkaloids in the treatment of parkinsonism has led to the introduction of a number of synthetic compounds in the past ten years. These have usually been employed in the place of the natural mixtures and have been reported by some as superior to the older forms of belladonna. The best that can be achieved by such substances is a partial relief of symptoms—there can be no cure or even restoration to near normal. One of the most conspicuous features of parkinsonism is the extreme variation of symptoms from hour to hour, as well as from day to day. Therefore, it is obvious that relative alleviation of symptomatology is not only difficult to evaluate from patient to patient, but even in the same individual during different periods of observation. These difficulties of evaluation are only emphasized by a perusal of the literature, which will attest that similar medications yielded completely opposite results, depending upon the observers and their criteria of measurement.

The purpose in this communication is to compare the results of Kemadrin to the available similar drugs, Artane and Pagitane, for a period of three to 20 months in 87 patients suffering from postencephalitic and other forms of parkinsonism. Fifty-one of the patients treated were those seen in the nerve outpatient department of the Massachusetts General Hospital. Thirty-six were private patients and were seen in the office setting. Both clinic and private patients received a battery of objective tests which have been previously described.[1] These tests were supplemented also by an evaluation of the newer combined test.[2] The patient's subjective opinion and evaluation of the medication, as well as that of members of the family, were taken into account. The neurologic assessment of one or both authors was integrated into the final decision as to the relative benefits of the preparation.

Kemadrin is procyclidine hydrochloride and its structural formula is shown in figure 1 for comparison with that of Artane and Pagitane. It is to be noted that the only chemical difference lies at either end of the molecule, and that the central part is identical in all three. In both Kemadrin and Artane the left-hand ring is a saturated 6 carbon one, but in Pagitane this is a 5 carbon saturated

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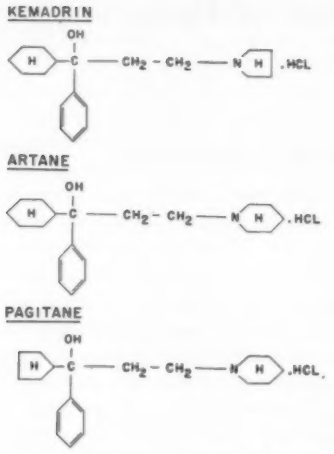

FIG. 1. The structural formulas of Kemadrin, Artane, and Pagitane. See text for comment on differences and similarities.

ring. Kemadrin, however, differs from both Artane and Pagitane at the right end of the formula where there is a pyrrolidine ring with 4 carbon and 1 nitrogen. In both Artane and Pagitane this position is occupied by a 5 carbon and 1 nitrogen ring called piperidine. The substance was available in scored 5 mg. tablets and in powder to prepare elixirs.

By means of gradual substitution, Kemadrin was introduced into the patient's therapy. Usually a dosage of 2.5 mg. three times a day was started in place of another medication (usually Artane or Pagitane). If this was well tolerated, the dosage increase was to 5 mg. three times a day and occasionally a 5 mg. dose was given before retiring. In most cases a dose of 5 mg. three or four times a day was well tolerated. In some cases, of course, smaller doses were employed. In others, patients tolerated a total dosage of from 40 to 60 mg. per day without unfavorable side effects. Less gastric discomfort was noted when the medication was administered with food in the stomach.

Side effects of Kemadrin were similar to those of Artane, consisting of dryness of the mouth, headache, visual blurring, and giddiness. Confusion and delirium with visual hallucinations occurred in the elderly patients if the dose was too large, which is similar to the side effects reported from any of the belladonna drugs in this age group. Kemadrin, however, produced fewer of these disturbances in older patients than did Artane. Rigidity was reduced but tremor was not appreciably affected.

In our series 38 patients were considerably improved with Kemadrin. Of these 38, 12 patients received beneficial results on Kemadrin alone. The other 26 patients achieved beneficial results with the Kemadrin when it was combined with Thephorin or Benadryl in doses of 75 to 100 mg. per day. Because of the frequency of administering Thephorin with Kemadrin, a mixture of 2.0 mg. of Kemadrin and 25 mg. of Thephorin for each 4 cc. was prepared. For the past four years we have tried various antihistaminics in combination with antispasmodics, such as Artane, Kemadrin, and Pagitane. Benadryl has been of some use, but the one that seems to combine most effectively has been the antihistamine, Thephorin. Thephorin produces less drying of the mouth and blurring of vision than Benadryl and partially neutralizes the slight dizziness and anorexia associated with the atropine substitutes. In approximately 50 patients out of a total of 75 who have been given Thephorin along with Artane, Pagitane, and Kemadrin, a very consistent subjective report is that Thephorin increased the effectiveness of the

antispasmodic. We have run control series where the drug was incorporated into an elixir against those in which the patients took the tablets of each together. We have found that 50 per cent of the patients who were given a choice of two such vehicles, elixir versus tablets, preferred the elixir. The reasons they gave for such a preference included greater ease of swallowing, less disagreeable effect on the stomach, greater effectiveness over a longer period of time, and in a few patients, perhaps no more than 10 per cent, freedom from disagreeable after-taste associated with some tablets. We have not been able to show any objective differences in the tests done on each patient that would correlate with the subjective reports of their individual preferences. However, it must be pointed out here that in some patients a far more individual and exact dosage schedule can be worked out with an elixir than with tablets. For example, there are some patients who are more comfortable if they have a slight increase in their after breakfast dose of medication, so they might take 5 cc. which would give them 2.5 mg. of Kemadrin and 31 mg. of Thephorin, as opposed to later doses of 2 mg. of Kemadrin and 25 mg. of Thephorin. It would not be possible to adjust the dosage so precisely using the tablets that are available.

Eighteen patients responded better to Artane, 11 patients responded better to Pagitane, and three patients appeared to be affected adversely by the Kemadrin medication. Seven patients received equal relief from Kemadrin, Artane, or Pagitane and used them interchangeably. Ten patients in the series were not benefited by either Artane or Kemadrin, and some other form of medication was utilized.

The 45 patients (52 per cent) who responded favorably to Kemadrin medication also showed a concomitant emotional elevation due to diminished rigidity. These patients were able to perform more readily daily tasks like combing their hair, dressing, and eating, which had previously been difficult chores.

Case 1.—A 45 year old unmarried female had had very severe influenza in 1918. Three years later she was diagnosed as having "encephalitis lethargica" and had difficulty remaining awake for a period of six weeks. In 1948 she noted slowness of movement, rigidity, and masking. In 1951 she was seen for the first time in the Parkinson Clinic of the Massachusetts General Hospital. She had previously been treated with Parsidol, Dexedrine, elixir of Lergigan, and Baminophenone with little success. In October 1952 Artane 2 mg. three times per day was started and some benefit resulted. This medication was continued until February 1954 when the patient noticed right-sided tremor and increased rigidity. Kemadrin was tried in small doses at this time and resulted in dramatic improvement. The patient's rigidity was reduced sufficiently to allow her to resume knitting. Walking was easier, tremor was diminished, and a general feeling of well-being resulted. At present she has been on Kemadrin for eight months, and on last examination there was no evidence of cogwheeling, rigidity, nor tremor. Objective tests were much closer to normal than before.

Case 2.—A 44 year old married female had had influenza in 1918 and again in 1941 which resulted in encephalitis. During the latter illness, the patient was comatose for several days, but no residual was noted following her recovery. A few months later oculogyric crises, tremor of toes, and drooling commenced. In February 1951 the patient first appeared at our clinic because of inability to grasp things. She was placed on Artane, scopolamine, and Dexedrine. This resulted in diminished incidence of oculogyric crises and ability to handle things better. In November 1953 she was given a trial of Kemadrin which caused the patient to become more rigid, yielded an increase in

tremor, and also produced paranoid ideation. She returned to a combination of Artane and Parsidol which again resulted in less rigidity, a disappearance of paranoid ideation, and slight diminishing of tremor. Objective tests showed some improvement also, and she has maintained this status up to the most recent examination.

DISCUSSION

In spite of the many quantitative measurements used in this study, we are fully aware of the inadequacies of such evaluation. A patient with parkinsonism who has not had any pharmacologic treatment or a patient who has been treated with marked side effects or no benefit can be measured and tested by the technics mentioned and a quantitative value obtained. After a week or two on an effective antiparkinson medication which does not produce too many side effects, a similar series of tests will invariably show objective improvement that can be measured, such improvement being obvious and clearcut. It is apparent to the clinically trained neurologist, however, that only approximately 25 per cent of the disabling symptoms of parkinsonism and the signs characteristic of it have been objectively modified by the medication used. Nowhere in the literature are there substantiating reports of complete disappearance of the symptoms and signs as occurs in diabetes, for instance, when adequate insulin adjustment is obtained.

In our extensive experience with the treatment of patients with parkinsonism over the past ten years, we have been disappointed in not being able to show *objective differences between two similar drugs that are both reasonably effective.* As we stated, we have always been able to show objective changes between *no treatment* and *an effective one.* For example, if a patient is objectively improved when Parsidol is used which controls both rigidity and tremor and then Benadryl is added to this drug because of the subjective complaint of dizziness, we have been unable to measure objectively the reported subjective improvement that the patient experiences. If, in addition, the patient complains of drowsiness and amphetamine is recommended which controls this symptom in a very definite manner, no objective signs in our tests are brought out. We would, therefore, not expect to find significant objective differences in the patients' response to similar drugs such as Artane, Pagitane, and Kemadrin. In spite of the fact that some patients would report a marked preference for one or the other because of a smoother beneficial effect or the total absence of disagreeable side effects, this improved state of health is not represented by objective increments in testing conditions. It will require a much larger series of cases and a much longer time to accumulate enough of the small details obtained in these objective tests before final quantitative results can be achieved.

However, because of the variabilities of patient response to already available parkinson medication, it is nevertheless worthwhile to implement further the armamentarium of the physician dealing with this disease, and thereby increase the practitioner's ability to prescribe a tailored therapeutic approach to each patient.

In comparing the results of effectiveness of Kemadrin (38 patients or 46 per cent) to the efficacy of Artane and Pagitane (29 patients or 33⅓ per cent), a difference of some 13 per cent is to be noted. This is certainly not a statistically significant differential, and it is certainly an indication that Kemadrin is as effec-

tive, in the long run, as is Artane and Pagitane. This, however, does not minimize its importance as another drug in the therapy of parkinsonism. Our results do not compare as favorably as those of Montuschi and his group[3] who found some 84 per cent of their series of 50 patients responding favorably to Kemadrin. Our observations agree with those of Sigwald[4] who found Kemadrin far more effective than any of the antihistaminics employed in parkinson therapy.

Utilization of combinations of Kemadrin to combat the rigidity and Parsidol[5] to reduce the tremor has been found to be an effective approach in a number of our patients.

SUMMARY

Kemadrin was employed in a series of 87 parkinsonism patients for periods of three to 20 months. Fifty-two per cent responded favorably to the drug with good symptomatic relief. A comparison with Artane shows that Kemadrin was 13 per cent more effective in this series.

Kemadrin may be employed to good advantage in combination with atropine-like drugs.

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Electrodiagnosis in Poliomyelitis

Alex J. Arieff, M.D. and Norman Dobin, M.D.

ELECTROMYOGRAPHIC examinations have been made in 62 patients with acute anterior poliomyelitis during and after the onset of the illness. The patients were divided into two groups. The first group included 33 patients in whom the paralyzed muscles began to recover soon after the onset of illness. In this group 91 muscles were examined at various times from two days to one year after the acute onset of paralysis. The second group consisted of 29 patients in whom no recovery was observed in the paralyzed muscles. In this group 94 muscles were examined at intervals ranging from two weeks to nine years after the onset of paralysis.

The electrical examinations included determination of rheobase, polar ratio, chronaxie, repetitive stimuli (interval curve), cathodal tetanus ratio, faradic response, and electromyographic observations.

RHEOBASE

No difference of diagnostic significance was noted in the median rheobase value plotted against time between the recovering and paralyzed muscles. The paralyzed muscles showed increased irritability to electrical stimulation for far longer periods than the recovering muscles. After years there was an increase in threshold of the paralyzed muscles to a median value of 8 ma. This was less than the median value for the rheobase of chronic cauda equina lesions (13 ma.) (figure 1).

CATHODAL TETANUS RATIO

The lowest median value of the cathodal tetanus ratio was observed 45 to 60 days following onset of paralysis. The median value in the recovering muscles was 3.5 which is within normal limits, while that of the paralyzed muscles remained less than 3, the lowest value for normal muscles. Years later, the median value of the cathodal tetanus ratio in paralyzed muscles was still around 2.5, corresponding to that in muscles of chronic cauda equina lesions. In spite of the seemingly irreversible paralysis, the cathodal tetanus ratio, by being above unity, indicates some degree of spontaneous neurotization (figure 2).

CHRONAXIE

In the group of recovering muscles, the chronaxie reached a median value of 20 msec. 60 days following the onset of paralysis. Then this value began to

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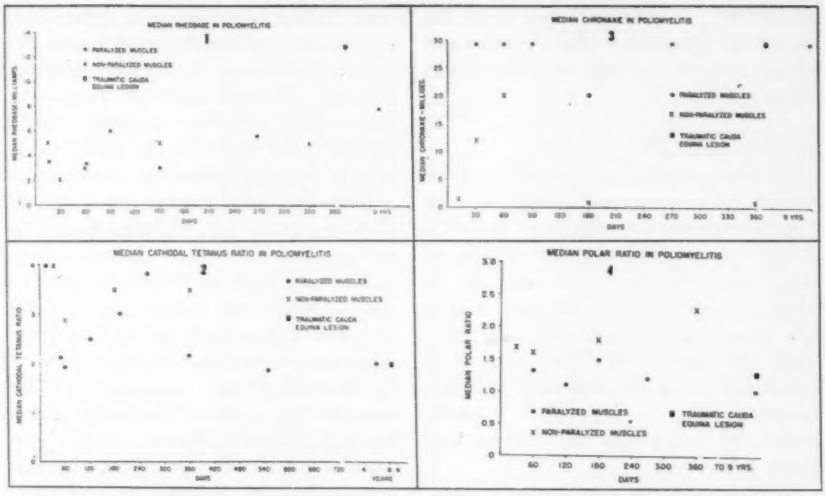


FIGS. 1-4. Results of electrical determinations of rheobase, cathodal tetanus ratio, chronaxie, and polar ratio in poliomyelitis.

drop until at 180 a median value of 1 msec. or less was observed, indicating practically complete reinnervation.

In the group of nonrecovering paralyzed muscles, the chronaxie rapidly increased so that a median value of 30 msec. was observed in less than 30 days after the onset of paralysis. This remained high, over 20 msec., nine years after onset of paralysis. This has been similarly observed in cauda equina lesions.

Thus the presence of a high chronaxie 180 days after onset of paralysis indicates a poor prognosis, since it so closely parallels a persisting clinical paralysis (figure 3).

POLAR RATIO

In the group with recovering muscles the median value of the polar ratio was between 1.5 and 2.0 up to 180 days after onset of paralysis. One year after onset it was about 2.3 or almost normal.

In the paralyzed muscles the median value was less than in the recovering muscles remaining under 1.5. Nine years after onset of paralysis the median value was 1.0, very close to the 1.3 (figure 4).

REPETITIVE STIMULI CURVES OR INTERVAL CURVES

The figures were analyzed from the standpoint of per cent of muscles having an abnormal or ascending curve. Normally the threshold for stimuli of 1 msec. with intervals of 1 msec., 5.0 msec., and 12 msec. follows a descending order.

In the group with recovering muscles, 56 per cent of the curves were ascending at 60 days following onset of paralysis. This per cent decreased with time so that 180 to 360 days after onset only 18 per cent of the curves were still ascending.

In the group with the paralyzed muscles, the per cent of ascending curves became high early, remaining close to

or at 100 per cent for years after the onset of paralysis. This corresponds closely with the findings in cauda equina lesions (figure 5).

FARADIC RESPONSE

In the group of recovering muscles, failure to respond to stimulation with faradic current was observed in 10 to 20 per cent of the muscles within 60 days after the onset of paralysis; in about 10 per cent, after 80 days; and in less than one per cent, one year after onset. In other words, the threshold to faradism may be elevated early but soon becomes close to normal in approximately 90 per cent of the muscles destined to recover.

In the group of permanently paralyzed muscles, 100 per cent of the muscles failed to respond to faradism early after onset of paralysis, and this persisted even up to nine years (figure 6).

ELECTROMYOGRAPHY

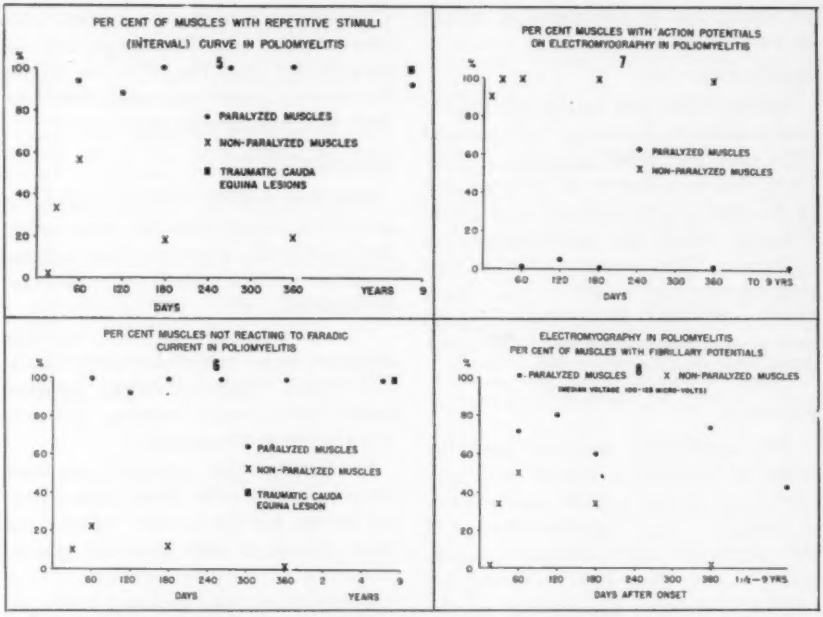
Pollock has summarized the literature with respect to spasm and the part electromyography has to do with spasm. Because it is very difficult to distinguish spasm from other types of contraction and contractures, electromyography was introduced as an objective method of indication of spasm. There had been numerous reports that spasm potentials have been demonstrated with the muscle completely relaxed. Attention has been called to the fact that it is probably difficult to relax a muscle in poliomyelitis that is not completely paralyzed because of the extreme pain, and some of these potentials would probably be due to a muscle splinting like in a fracture of a long bone. Bouman and Schwartz stressed the occurrence of cocontraction for the reversal of reciprocal innervation. They felt there was reflex spasticity more than one would see in voluntary movement in acutely paralyzed muscles. Buchtal, however, found that these action potentials to passive stretch varied from epidemic to epidemic or absent in some epidemics. Synchronous activity has been considered diagnostic of poliomyelitis but Buchthal found this to be present in other diseases of the nerve roots such as in amyotrophic lateral sclerosis and progressive muscular atrophy. Disturbance of normal reciprocal innervation has also been observed by Watkins, Frazer, and Schwab. They consider this a part of the acute picture in poliomyelitis. Harrel, Mead, and Mueller did not find persisting electrical activity in 100 children paralyzed by poliomyelitis in the St. Louis City Hospital epidemic in 1949.

With respect to the three types of activities supposedly characteristic of spasm: 1) spontaneous activity is rarely if ever found in poliomyelitis in the limb muscle if properly postured; 2) synchronous activity occurs in other conditions; and 3) cocontraction of antagonist muscle cannot be said to be an abnormalilty since it occurs without shortening either group of agonist and antagonist in cerebellar disorders.

Action potentials
(accompanying voluntary effort)

In patients with recovering muscles, 100 per cent of the muscles tested showed the presence of action potentials associated with voluntary effort within 30 days after the onset of paralysis, some showing this even before that time. The amplitude of these action potentials ranged from 45 to 2,500 microvolts (figure 7).

In the permanently paralyzed muscles,



FIGS. 5-8. Results of electrical determinations of repetitive stimuli, faradic response, action potentials, and fibrillary potentials in poliomyelitis.

practically 100 per cent had no action potentials up to nine years following onset of paralysis (figure 7). It should be emphasized that no potentials were elicited in the muscles in spite of pain. We feel that this observation eliminated any type of so-called spasm potentials in the muscles paralyzed.

Fibrillary potentials
(denervation potentials)

In the recovering group of muscles fibrillary potentials representing fibrillary activity were detected in 30 per cent of the muscles 30 days after onset of paralysis, and in 50 per cent 60 days after onset. The number of muscles showing fibrillary activity decreased slowly after this, so that 30 per cent showed this activity 180 days after the onset, and none one year after. The amplitude of these fibrillary potentials ranged from 10 to 55 muv. The presence of fibrillary activity may be the only evidence of a muscle previously affected by poliomyelitis.

The presence of fibrillatory muscles was greater in the permanently paralyzed than in the recovering group, 70 per cent of the muscles showing this activity at 60 days, 80 per cent at 120 days, and 70 per cent one year after the onset of the paralysis. Over 40 per cent of the muscles were still fibrillatory one and a half to nine years after onset. The amplitude of the potentials ranged from 10 to 200 muv. (figure 8).

The median voltage value of fibrillation was higher than usually document-

ed, being 100 to 125 muv. as against 50 muv.

Spontaneous units

Spontaneous units except for fibrillation included fasciculation, v waves, and other units just called spontaneous units. They were recorded in 15 to 25 per cent of the muscles examined and had amplitudes up to 200 muv. and durations up to 2 msec. They were not found in four patients one and a half to nine years after onset. We never observed high voltage spontaneously firing units as described by Grundfest.

DISCUSSION

The information obtained from the study of kinetics of stimuli with galvanic and faradic current and electromyography is very important because of the diagnostic and prognostic significance at any given time following the onset of paralysis. The findings of the electrical examination in poliomyelitis are similar to those of other lower motor neuron lesions, as in peripheral nerves and in cauda equina lesions.

Although 62 patients were examined in this study, serial examinations were not available in every patient. Some serial examinations at stated intervals in a large group of patients would give more concise data. Such studies should be made in the future to amplify the present report.

Information of prognostic significance obtained with the use of faradic current in this study was of such critical value that the use of this relatively simple apparatus should not be neglected, particularly when more elaborate and expensive apparatus such as a square wave stimulator or electromyograph are not immediately available. It is our feeling that more experimental work should be done with the faradic wave forms.

SUMMARY

Sixty-two patients with 94 paralyzed and 91 recovering muscles were examined electrically at various times ranging from two weeks to nine years after onset of paralysis.

The examination included galvanic rheobase, polar ratio, chronaxie, repetitive stimuli (interval) curves, cathodal tetanus ratio, faradic response, and electromyographic observations.

For the most part, galvanic data were consistent with other lower motor neuron lesions, but the faradic response was most consistent with eventual clinical picture of recovery or paralysis.

Electromyography revealed active potentials in recovering muscles a few weeks after paralysis. None were present in the chronically paralyzed muscles even in the presence of marked neuromuscular pain, that is, no spasm units were found. Fibrillary potentials were present in both groups but disappeared in most of the recovered group at the end of a year, but were present in 40 per cent of the chronic muscles years after paralysis.

The median fibrillary denervating voltage was 100 to 125 muv., which is greater than those usually encountered. High voltage spontaneous units were not observed.

This work should be repeated with serial studies.

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■ It must be too obvious that the evidence adduced as to the nature of the proximate and occasional causes of this disease, is by no means conclusive. A reference to the test therefore which will be yielded by an examination of some of the more prominent symptoms, especially as to their agreement with the supposed proximate cause, is more particularly demanded. Satisfied as to the importance of this part of the present undertaking, no apology is offered for the extent to which the examination is carried on.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817

CASE REPORT

Hydranencephaly

Charles M. Poser, M.D., Faith C. Walsh, M.D. and Labe C. Scheinberg, M.D

HYDRANENCEPHALY is a relatively uncommon congenital anomaly of the central nervous system, consisting of complete or nearly complete absence of the cerebral hemispheres with a relatively normal sized skull. The space is filled with fluid resembling cerebrospinal fluid. Such a defect is usually not noticed in the newborn since little or no evidence of cerebral function is manifest at that time. It is only when the child fails to develop the usual postural and locomotor patterns expected with normal growth that attention is directed toward the possibility of a defect in development of the nervous system.

Since Cruveilhier's[1] first report of what he called "hydro-anencephaly" there have been approximately 30 such cases recorded in the literature under various names. The French have preferred using the term "hydrocéphalie anencéphalique," while American authors have adopted the term "hydranencephaly."[2,3] Yakovlev and Wadsworth[4] included this condition in their group of "schizencephalies," while others used the more descriptive term "child without a forebrain."[5]

Only five of the reported cases were studied by ventriculography, and there are no reports on lumbar encephalography or arteriography in any of these cases.

An infant admitted to the Neurological Institute and diagnosed clinically as a case of hydranencephaly has been studied by all three methods.

It is the purpose of this paper to present the findings in this case, because of the possible bearing they may have on the understanding of the etiology of this condition.

CASE REPORT

An eight month old white male was admitted to the child neurology service of the Neurological Institute on September 28, 1953 because of apparent mental retardation.

The patient was the second child of a 28 year old mother and was born at term following an uncomplicated pregnancy. Labor was uneventful and lasted six hours. The child was a vertex presentation. After delivery, the mother was told that a twin fetus had died in utero after two or three months' gestation.

The infant appeared normal at birth and weighed 8 pounds, 1 ounce. He breathed

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spontaneously. It was noted that he cried almost constantly during the early weeks of life and numerous changes in diet were tried without result. The child appeared to have some sucking difficulty and was unusually irritable. During the first two months of life, he was able to hold up his head from the prone position and was observed to stick his fingers in his mouth. He often "stiffened out" for five or ten minutes, especially after feedings, crying loudly with relief after eructation or passage of flatus. These episodes continued up to the time of admission. At the age of three months it was noted that he could not control his head when held in the sitting position. He did not follow light nor seem to recognize his parents. He was observed to have a vacant stare on many occasions. At seven months the child appeared to smile and became more attentive to its surroundings. No recognizable sleep pattern had yet become established. There were no previous illnesses. Diphtheria, tetanus, and pertussis immunizations had been completed, but the child had not been vaccinated.

The family history revealed instances of twinning on both paternal and maternal sides. There was no consanguinity. Both parents were healthy, as was also a normal six year old sibling. A distantly related paternal cousin was said to have been mentally retarded.

On admission, the patient was an obese child with a slightly enlarged head who cried almost continually during waking periods. The temperature was normal. Height was 27 inches, weight 25 pounds 6 ounces, head circumference 20.5 inches, (six standard deviations above normal), chest circumference 19.5 inches. The anterior fontanelle was soft. The skull gave forth a tympanitic note on percussion. There were four incisors. Except for an exaggerated lumbosacral curve and an undescended right testicle, the general physical examination was unremarkable.

On neurologic examination the child was irritable and uninterested in his surroundings. There was marked head lag and the child was unable to control his head when held in the sitting position. He was unable to sit up unsupported. All extremities moved spontaneously and were withdrawn from pinprick. There was increased resistance to passive movement of all muscle groups. Deep tendon reflexes were equal and normally active. There were no abdominal or cremasteric reflexes and the plantar responses were flexor bilaterally. Pupils were equal and responded promptly to light. Eye movements were random and uncontrolled, and the child did not follow light. There was occasional internal rotation of the left eye and the eyes were not observed to move upward or to the left. The optic fundi were well visualized and the optic disks appeared sharply outlined and slightly pale. There was occasional undulatory nystagmus. No apparent abnormality of the rest of the cranial nerves was observed. The child was observed to follow a conspicuous moving object and to retain grasp of a ring placed in his hand. Occasionally he seemed to smile when held. There were frequent extensor spasms during which the extremities could be flexed only with difficulty. The child took his feedings well. No definite sleep pattern could be established.

When the child was placed in a very dark room and a light held below the occipital protuberance, the light was seen to glow through the calvarium and fontanelles and a red light appeared through the pupils.

Laboratory findings: hemoglobin 11.2 gm.; red cell count 3.65 million; white cell count 6,000, with 49 per cent polymorphonuclear cells; urinalysis normal; blood and cerebrospinal fluid Mazzini negative; Mantoux negative to 1:100; lumbar cerebrospinal fluid cell count two white cells, protein content 32 mg.; intracranial cerebrospinal fluid protein 29 mg. per cent.

Roentgenograms of the skull were reported as showing a larger than average skull with a configuration suggesting hydrocephalus. X-ray films of the chest were normal. Roentgenograms of the lumbosacral spine were reported as showing sacralization of the fifth lumbar vertebra.

An electroencephalogram was performed but no electrical activity could be recognized on the record.

On the Gesell developmental schedule, the child was rated at the one month level.

On October 2, 1953, under Avertin anesthesia, a lumbar pneumoencephalogram was performed with the injection of 30 cc. of oxygen (figures 1 and 2). Then 100 cc. of air was injected through the lateral angles of the anterior fontanelle after removal of 105 cc. of clear colorless fluid. The child tolerated these procedures quite well.

On October 5, 1953, again under Avertin anesthesia, a left common carotid arteriogram was performed with Thorotrast. Immediately following this, 275 cc. of blood-tinged fluid was removed from the cranial cavity through the anterior fontanelle and replaced with air. Appropriate roentgeno-

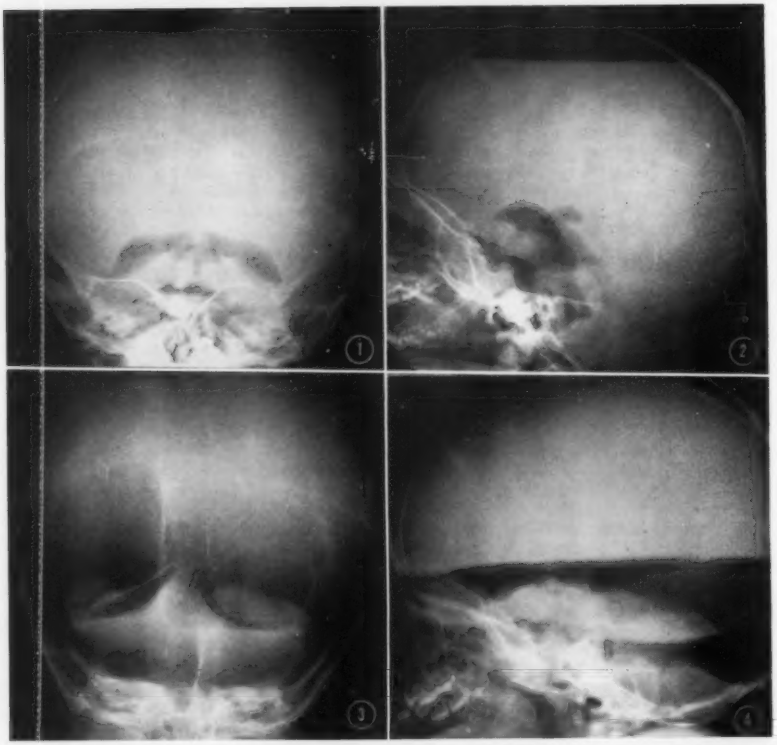

FIG. 1. Lumbar pneumoencephalogram, anteroposterior view. Outline of rudimentary ventricular system. The air seen under the calvarium at the top of the photograph was injected through the fontanelle. There is no communication between the ventricular system and the fluid-filled cranial cavity.

FIG. 2. Lumbar pneumoencephalogram, lateral view. Outline of rudimentary ventricles.

FIG. 3. Intracranial air encephalogram, posterior anterior view. The air was injected through the anterior fontanelle. Picture taken with child held upside down. The outline of the cerebral mass can be clearly seen.

FIG. 4. Intracranial air encephalogram, lateral view. Picture taken wtih child held upside down.

grams were then made (figures 3 and 4 for intracranial air injection, figures 5, 6, 7, and 8 for arteriogram). Again the child withstood the combined procedures without untoward effects.

The roentgenograms obtained after injection of oxygen via the lumbar route and injection of air intracranially via the anterior fontanelle were reported as follows: "The pneumoencephalogram films show the presence of an enlarged fourth ventricle and a normal size aqueduct. If anything, the aqueduct is larger than average. There is a shadow resembling a third ventricle and a foramen of Munro. Two collections of air are seen on each side of the midline which resemble rudimentary lateral ventricles, but it is obvious that there is very little if any tissue above the roof of the ventricles. If one superimposes the films taken following injection of air from below and those made in the upside-down position following the injection of air from above, there is no soft tissue present between the superior outline

of what seem to be rudimentary ventricles and the top of the soft tissue shadow representing the brain tissue. Probably a very thin membrane actually exists forming the roof of the ventricles. No air was seen in the intracranial cavity following injection of air via the lumbar route. There is no connection between the rudimentary ventricular system and the rest of the cranial cavity."

The arteriographic films were reported as follows: "The films demonstrate good filling of the internal carotid artery. There is a rather large ophthalmic artery present. A large posterior communicating artery is also present and retrograde filling into the basilar artery is seen. Good filling of both posterior cerebrals and superior cerebellars is noted, but the posterior cerebral arteries turn downward instead of continuing their normal upward course. The middle cerebral arteries are filled and, since compression was applied to the opposite side, both sides are visualized. The middle cerebral arteries are symmetrically placed and they make the usual turn outward and upward, but then no vessels are seen to go above where they would ordinarily ascend on the surface of the cerebral hemispheres. This would indicate that there is no evidence of a cerebral hemisphere, or that at least the parietal and frontal lobes are absent. The anterior cerebral arteries cannot be visualized adequately but there is a thin branch extending from the expected site of the bifurcation of the

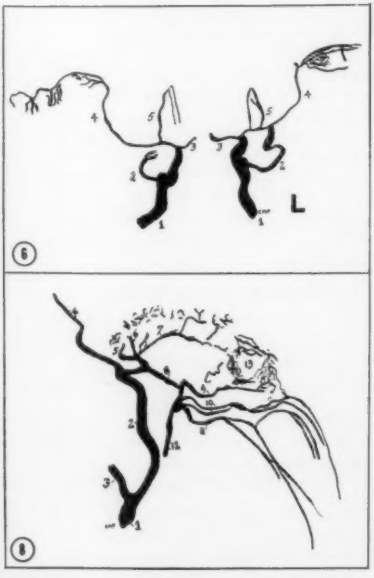

FIG. 5. Left common carotid arteriogram, anteroposterior view. Compression of right common carotid. There is filling of the internal carotid systems on both sides and of the external carotid on the left.

FIG. 6. Tracing of internal carotid system as shown in figure 5. Left carotid arteriogram, anteroposterior view. 1. Internal carotid; 2, ophthalmic; 3, anterior cerebral; 4, middle cerebral; 5, posterior cerebral.

FIG. 7. Left common carotid arteriogram, lateral view. There is filling of both the internal and external carotid systems, as well as retrograde filling of the basilar artery. Air is still present in the frontal region from previous encephalogram.

FIG. 8. Tracing of internal carotid system as shown in figure 6. Left carotid arteriogram, lateral view. 1, common carotid; 2, internal carotid; 3, external carotid; 4, ophthalmic; 5, anterior cerebral; 6 and 7, branches of middle cerebral; 8, posterior communicating; 9, left posterior cerebral; 10, superior cerebellars; 11, right posterior cerebral; 12, basilar; 13, choroid plexus.

internal carotid artery which could be the trunk of the anterior cerebral artery. No definite filling of the ascending branches of the anterior cerebral artery can be seen on any of the films. There is no trace of a pericallosal branch. On the lateral serialographic films an ascending frontoparietal branch, a suggestion of an angular branch, and a posterior temporal branch of the middle cerebral artery can be made out. It is also interesting to note that there are numerous fine vessels which have the characteristic configuration and appearance of a choroid plexus. They seem to be filled mostly through the branches coming off the basilar artery, but there is some connection with the anterior circulation.

"There is unusually good filling of the branches of the external carotid artery and it is obvious that the speed of circulation in the external carotid artery is as fast as that in the internal carotid artery, which is ordinarily not the case. The distribution of the branches of the external carotid artery is entirely normal."

Following all these procedures, the child's head did not transilluminate any more; this was believed due to the admixture of blood with the intracranial fluid.

The child was discharged on October 10, 1953.

DISCUSSION

A slightly macrocephalic, retarded eight month old child was diagnosed as a case of hydranencephaly with the help of transillumination of the head. Illustrations of the resulting effect have been published previously[3] and it has been said that this appearance is pathognomonic for this condition. Confirmation was obtained by intracranial air injection, with demonstration of a small soft tissue shadow at the base of the skull which presumably represents the existing brain tissue. Further investigation was carried out by lumbar pneumoencephalography and carotid angiography with the results summarized above.

Cruveilhier[1] first described a fetus without a forebrain and called it "hydroanencephaly." Edinger and Fischer[6] believed that this condition was the result of extreme porencephaly. Cohn and Neumann[7] agreed with this theory and felt that it was based on a vascular insufficiency. Marburg and Casamajor[5] also subscribed to the vascular theory but believed it was due to venous stasis and thrombosis of the deep cerebral veins. Crosby[8] felt that the brain developed normally until the fifth fetal month and at this time there was a regression of the cerebral hemispheres. Ford[9] stated that hydranencephaly is merely the endpoint of extreme internal hydrocephalus. Finally, Yakovlev and Wadsworth[4] traced an anatomic continuum between these extreme cases with hydrocephalus and less severe cases with congenital clefts in the cerebral mantle, and they designated the condition as "schizencephaly." With the several theories in mind, it is worthwhile to review the findings in the present case.

Pneumoencephalography by way of the lumbar route demonstrated what appeared to be rudimentary lateral ventricles with a membranous roof. Bettinger[10] mentioned encountering such a membrane which "obscured the view of the anterior and middle fossae" in a patient he examined at post mortem. No cerebral hemispheres were present. The films obtained after intracranial air injection are very similar to those described by Hamby, Krauss, and Beswick[3] and Watson.[11] They used the term ventriculography without producing evidence that the ventricles were actually entered. In the present case, it is only possible to say that air was injected intracranially by way of the anterior fontanelle. However, since rudimentary lateral ventricles were demonstrated by lumbar air injection, it was obvious that air was not introduced into them from above. No connection existed between the lateral ventricles and the intracranial cavity.

The angiographic findings are of considerable interest in view of the almost normal but miniature appearance of the internal carotid arterial system. In connection with this it is worth mentioning

that in Johnson, Warner, and Simond's[12] case the authors noted the absence of the internal carotid arteries on postmortem examination. Hamby, Krauss, and Beswick[3] mentioned that in three of their seven cases "the anterior and middle cerebral arteries were functioning efficiently although understandably smaller than normal since their areas of supply were practically abolished." These arteries were seen at the bottom of the cavity which had been drained of fluid after opening a thin membrane lining the dura. This would seem to have been a situation analogous to the one existing in the present case. Here both the anterior and middle cerebral arteries were present, although only a rudiment of the former could be identified. The posterior cerebrals were well visualized but their course was anomalous distally. The normal appearance of the external carotid circulation would seem to indicate that the dura was normally present and that its supply of blood was not affected.

From our findings in this case it is obviously impossible to say what the relationship in time is between cerebral agenesis and the development of the cerebral blood supply, much less about cause and effect. However, in the presence of a grossly normal cerebral vasculature, perhaps some clue can be obtained by comparison with the work of Vogel and McClenahan,[13] who found in their study of anencephaly that anomalies of the major arteries developing some time after the third to fifth week of fetal life may be an important factor in the pathogenesis of anencephaly in human beings.

It is also evident from the angiographic findings in this case that hydranencephaly is not the end result of a severe internal hydrocephalus.

The appearance of the cerebral blood vessels is entirely different. In hydrocephalus the branches of the internal carotid artery are normal in appearance and general distribution, but they are stretched over the surface of the cerebral hemispheres instead of being restricted to a small area at the base of the skull as they are in hydranencephaly.

It is suggested that further study of similar cases with air and dye may help to differentiate between conditions that are called hydranencephaly clinically but may have diverse pathogenesis.

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CASE REPORT

Spontaneous Dislocation of the Atlanto-Axial Joint in Rheumatoid Spondylitis

Recovery from Quadriplegia Following Surgical Decompression

Murray E. Margulies, M.D., Isadore Katz, M.D. and Meyer Rosenberg, M.D.

SPONTANEOUS SUBLUXATION of the atlanto-axial joint is a rare clinical entity which was first recognized in 1830.[1] It has been described chiefly in children, in whom it occurs most commonly as a complication of infections about the mouth, nose, throat, and neck, such as nasopharyngitis, tonsillitis, and mastoiditis. It has also been observed in association with the exanthemata and in rheumatic fever. Rarer instances have been reported in association with actuall destructive diseases of the vertebrae or their ligamentous attachments. Kornblum, Clayton, and Nash[2] recently reported four cases of dislocation of the cervical spine occurring in rheumatoid spondylitis. Two of these cases involved the atlanto-axial joint, the third occurred at the C-5, C-6 level, and the fourth at the C-6, C-7 level. Earlier cases in which the etiologic factor suggested rheumatoid arthritis were reported by Ely,[3] Staumers and Frazier,[4] and Rand.[5]

The term, Marie-Strumpell's disease, originated following Strumpell's report in 1897 of cases with ankylosis of spine and hip joints, and Marie's report in 1898 of six cases with complete fusion of the thoracic and lumbar spine. A more precise scientific term is that of rheumatoid spondylitis, now accepted as a synonym for Marie-Strumpell's disease.

In those cases associated with rheumatoid arthritis the dislocation is usually insidious in onset and traction therapy may be effective if instituted early. When traction and other therapeutic measures fail, and where the signs and symptoms of cord compression persist or are progressive, surgical intervention should be attempted. A case in which successful surgical fusion of the cervical spine was performed has been reported by Rand,[5] whose patient showed progressive subluxation of the atlas with development of a Brown-Sequard syndrome. Titrud and co-workers[6] recently reported the first case in which an emergency cervical cord decompression was performed successfully in a patient who developed quadriplegia as a result of spontaneous atlanto-axial dislocation following a sore throat.

Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 30, 1954.

From the section of neurology and the department of radiology, Veterans Administration Hospital, Brooklyn.

The case which forms the basis for this report is an additional instance in which a successful decompression operation was done to relieve high cervical cord compression following atlanto-axial dislocation. This was in a patient with chronic rheumatoid spondylitis, in whom traction therapy failed to give sustained relief of signs and symptoms of cervical cord compression.

CASE HISTORY

A 30 year old negro male hospital attendant, well developed and fairly well nourished, was admitted to the Veterans Administration Hospital, Brooklyn, on November 7, 1952. He complained of severe pain at the nape of the neck, radiating upward to the back of the head, with inability to rotate the head or flex the spine. There was also difficulty in opening the mouth because the chin rested on the chest.

The illness had begun in 1935 when the muscles of the neck became stiff and painful. A few months later he noticed difficulty in flexing his spine, and at the same time the lower back became painful and stiff. His symptoms were rather mild until 1944 when he first experienced difficulty in rotation of the head to the right and left. At that time he began to walk with the head tilted forward and rotated to the left while the neck remained flexed. He sought no medical advice until 1949 when roentgenographic examination showed paraspinal ligamentous calcification with ankylosis of the apophyseal joint of cervical spine.

These symptoms became more severe, and in September 1952 the patient was treated with penicillin and ACTH. In October 1952 there was a rapid progression of these symptoms with development of weakness of the right hand and right foot. At this time he developed urinary urgency. A few days later while taking a bath, he noticed that he could not perceive heat on the left side of his body as well as on the right side. The pain in the muscles of the neck became more severe and he entered the hospital.

The physical examination was negative except for the following: The head was tilted to the left side, the chin rested on the sternum, and the spinal column was rigid. There was atrophy of the musculature of both shoulder girdles, more marked on the right side, with atrophy of the small muscles of the right hand and of the extensors of the forearm producing a wrist drop. There was marked motor impairment of the right upper extremity and to a lesser degree of the right and left lower extremities. The left upper extremity was least involved. The deep reflexes in the right upper extremity were not elicited, while in the lower extremities they were increased more so on the right. In addition, there was spasticity, ankle clonus, absent abdominal and cremasteric reflexes on both sides and a Babinski toe sign on the right side only. The response to pinprick was markedly impaired on the left side of the body up to C-4, although C-4 was spared. Above this, within the segmental distribution of C-3 and C-2 on the left side, the appreciation of the pin-point was diminished but to a lesser degree than over the rest of the body. The face was spared and light touch was appreciated well throughout the entire body.

The picture was that of a modified Brown-Sequard syndrome. The radiographic examination of the entire spine showed demineralization, paraspinal ligamentous calcification, apophysial joint obliteration—all characteristic of ankylosing rheumatoid arthritis. The sacroiliac joints were almost totally ankylosed (figure 1). In addition, the cervical spine revealed a complete forward displacement of the first cervical vertebrae on the second (figure 2).

Course in hospital: A few days after admission to the hospital, the patient developed complete quadriplegia. There were several episodes of urinary incontinence. Crutchfield tongs, placed 3 centimeters anterior to the usual position, were applied in order to exert a rotary effect as well as traction upon the cervical spine. This was followed by immediate improvement of the position of the head and gradual neurologic recovery. However, one week after the application of the tongs, the patient became rapidly worse, developing a quadriplegia. The line of traction had to be readjusted and this again was followed by improvement. A few days later a neck brace was applied. The therapeutic results of the brace were unsatisfactory, however, with increased motor weakness and respiratory difficulties ensuing. The Crutchfield tongs were re-applied but again the patient became quadriplegic. The neck brace was then quickly replaced and the tongs readjusted. The sudden quadriplegia was partially relieved.

It now became obvious that it would be impossible to obtain a spontaneous fusion of the spine with permanent relief of symptoms, and that an exceedingly narrow margin of safety existed with traction. Therefore the patient was prepared for a laminectomy as follows: A Minerva plaster jacket was applied and the Crutchfield tongs with an attached turnbuckle were affixed to the overhead bar of an inverted U-shaped device, the arms of which were attached to the Minerva jacket.

Operative procedure: A preliminary tracheotomy was done followed on February 20, 1953 by a laminectomy performed under local anesthesia. At operation, it was found that the atlas was firmly fused to the occiput. Motion was present between the atlas and the axis. The remaining portion of the exposed cervical spine, that is, C-2, C-3, and C-4 were ankylosed. A laminectomy of C-2 was done. The dura appeared a dull grayish-blue, and pulsations were absent. The dural sac was compressed from both sides by two exostoses, which were carefully removed until the dural sac assumed a normal contour and pulsations of the dural sac were noted for the first time. Following this, two long cortical, cancellous bone grafts were placed in such a position as to fuse the occiput and the atlas with C-3 and C-4 (figure 3). The postoperative course was uneventful.

During the course of the operation, and immediately following removal of the exostoses, immediate improvement of the motor power of the right lower extremity was noted. Sensory examination done the following day revealed that the pin point was appreciated by the patient better than before the operation. On the fourth postoperative day, partial return of motor power of the right upper extremity was noted. The patient then began to move his fingers. Two days later, the patient was able to move his lower extremities well and began to dorsiflex the right wrist. The response to pin prick was practically the same on both sides of the body, and urinary urgency disappeared. The patient began to walk 12 days after the operation, and three weeks later his gait was practically normal. Increase of muscle volume of the intrinsic musculature of the right hand was noted thereafter, and by June the interosseous spaces of both hands were equal. The plaster jacket was removed on July 20, 1953 and after this the patient walked with a neck brace for two months. At present, he is entirely symptom-free.

DISCUSSION

In some cases of spontaneous cervical dislocation which developed as complications of the upper respiratory tract or deep cervical tissue infections, it is felt that the ligaments which maintain the alignment of the vertebrae become loosened as a result of decalcification of the bony structures. This decalcification, it is generally agreed, results from the hyperemia induced in the tissues by the infectious process. Thus, when their attachments are loosened the ligaments become relaxed and subluxation takes place. Another explanation of the pathologic process taking place was first offered by Whittek,[7] who maintained that a "metastatic effusion" distended the small capsules of the atlanto-axial joints and thereby relaxed the ligaments which maintained the normal stability of these joints.

Pathologic material obtained from the site of dislocation has hitherto been unavailable except in the case reported by Titrud and his co-workers. In their case the extradural tissue removed at operation showed an inflammatory reaction with perivascular infiltration throughout the fibrous portion of the tissue. In a section of bone removed, no inflammatory reaction was seen although the bone was described as soft."

In the present case, histologic examination of bone removed at operation was reported by the pathologist as follows: 1) Microscopic examination revealed spicules of bone with replacement of bone marrow by fibrocollagenous tissue containing a dense infiltrate of polymorphonuclear leukocytes, lymphocytes, occasional plasma cells, and monocytes (figure 4). 2) Section showed synovial tissue containing monocytes and proliferating fibroblasts. 3) Section of muscle showing atrophy of muscle fibers with some loss of striation and edema of the interstitial tissue.

Thus, in the case of Titrud and co-workers as well as in our case, there is evidence that rheumatoid arthritis involves extra-articular bone as well as the synovial membrane and other articular soft tissues. In this connection, it is interesting to note that Baggenstoss, Bickel, and Ward[8] found, in a case of rheumatoid arthritis studied at necropsy, that granulomatous nodules were present in a vertebral body showing roentgenographic evidence of a compression fracture. In this case the granulomatous nodules, pathognomonic of rheumatoid arthritis, were also found in the common loca-

FIG. 1. Radiographic examination of the spine showing demineralization, paraspinal ligamentous calcification, apophysial joint obliteration - all characteristic of ankylosing rheumatoid arthritis. The sacroilliac joints were almost totally ankylosed.

FIG. 2. Cervical spine revealing a complete forward displacement of the first cervical vertebrae on the second.

FIG. 3. Bone graft showing fusion of the occiput and the atlas with C-3 and C-4.

FIG. 4. Microscopic examination revealed spicules of bone with replacement of bone marrow by fibrocollagenous tissue containing a dense infiltrate of polymorphonuclear leukocytes, lymphoctyes, occasional plasma cells, and monocytes.

tions such as the synovial membranes, pericardium, myocardium, and subchondral bone. These authors emphasize that this granulomatous process commonly seen in the subcutaneous tissues of patients with rheumatoid arthritis may be the cause of a destructive process in a vertebral body and should be considered in the differential diagnosis of destructive lesions of the spinal column. In support of this, Guest and Jacobson[9] found roentgenographic evidence of osteopathy of the vertebral bodies in seven out of 90 patients with rheumatoid spondylitis. These authors stated, moreover, that the evidence suggested that these changes are inflammatory in nature.

SUMMARY

1. The case history of a patient with rheumatoid (Marie-Strumpell) spondylitis who developed quadriplegia following spontaneous dislocation of the atlanto-axial joint is presented.

2. Successful treatment of the high cervical cord compression by means of laminectomy and fusion of the occiput and atlas with a third and fourth cervical segments is described.

3. Pathologic material taken from the site of subluxation is presented.

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NEWSLETTER

APRIL 1955

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

ANA to Meet in Chicago The American Neurological Association will hold its 80th annual convention in the Palmer House, Chicago (June 13-15), which is its first annual meeting to be held outside of Atlantic City since the San Francisco meeting in 1946. The scientific sessions will occupy the morning, afternoon, and evening of June 13; morning and afternoon of June 14; and the morning session only of June 15. The annual dinner will be held on Tuesday evening, June 14.... Communications should be forwarded to Dr. H. Houston Merritt, Secretary-Treasurer, 710 West 168th Street, New York 32.

Canadian Neurological Society To Convene in Toronto Following as a timely sequel to the American Neurological Association program is the seventh annual meeting of the Canadian Neurological Society, which will be held on June 16-19 in Toronto. The AAN and other U. S. national neurologic and neurosurgical societies are being invited to send two representatives to attend as guests at the scientific sessions and the social events of the Canadian group. Members of the Canadian Society also may extend invitations to American or Canadian non-members to attend the social events as the guest of the member, through the secretary of the society. These arrangements must be made in advance. In addition, all Canadian and American physicians interested in neurology may attend the scientific sessions by registering at the time of the meeting. Members or visitors should make their own arrangements for accommodations in Toronto through Glenn Sawyer, M. D., Chairman, Committee on Housing, 244 St. George Street, Toronto 5, Ontario.... The scientific sessions will be held at the Sunnybrook Hospital in North Toronto, which can be reached from the downtown hotels by subway, bus, or taxi. A Thursday afternoon symposium will consider the diffuse projection pathways of the reticular system and the centrencephalic concept. Friday and Saturday are reserved for individual papers of 20 minutes followed by 10 minute discussions. Half of the scientific program will be provided by British neurologists through Dr. Paul Sandifer of London. The social events include cocktails at the York Club (June 16) and the annual dinner at the Royal York Hotel (June 18).

International Reunion In Paris The 20th Annual International Neurological Reunion, organized by the French Neurological Society (Societe Francaise de Neurologie), will take place in Paris (June 7-8). The reunion will be devoted to a presentation of studies on the neurologic aspects of collagen diseases. The program, which is under the direction of Prof. Raymond Garcin, will include reports by H. Roger, Poursines, and J. Roger (on periarteritis nodosa), and by R. Garcin, J. Lapresle, J. Gruner, and Scherrer (on myositis). The reunion also will provide occasion for the presentation of a commemorative volume (Livre Jubilaire) to the distinguished French neurologist, Andre-Thomas.... Associate members and honorary foreign members of the French Neurological Society who intend to participate in the meeting should register with the secretary-general before May 1. Physicians who are not members of the French Society may request registration in the reunion from the secretary-general. A fee of 2,000 francs is required for such registration, payable to the French Neurological Society, Mme Sorrel-Dejerine, Treasurer, 123 rue de Lille, Paris (VIIe).... All neurologists desiring to participate in this international reunion should communicate before May 1 with the Secretary-General of the Society, Dr. Jean Sigwald, 68, boulevard de Courcelles, Paris (XVIIe).

* * * * * *

Haymaker Joins German Diplomatic Mission On February 6 a special plane carried six American leaders in the public health field from Idlewild Airport to the Federal Republic of Germany as guests of the German government. Among them was Webb Haymaker, chief of the neuropathologic section of the Armed Forces Institute of Pathology. The broad purpose of the tour was to give American public health officials an opportunity to become acquainted with present-day life and institutions in Germany. The tour is part of an exchange program with the U. S. inaugurated in 1952. Following an official welcome in Bonn, Haymaker and others in the party visited several German cities, including West Berlin.... In a special dispatch, Haymaker commented favorably on interesting conferences held with neurologic scientists in Bonn, Hamburg, Kiel, Frankfurt, Giessen, Neustadt, Wurzburg, Freiburg, and Munich. He made special mention of an interview with R. Jung in Freiburg, whose collaborator, R. Hassler, a neurosurgeon, is doing interesting work on the thalamus with stereotatic technic for controlling symptoms in parkinsonism, phantom pain following limb amputation, and dystonia musculorum deformans.... Haymaker returned to the U. S. March 20, via Brussels, Antwerp, Wiesbaden, Heidelberg, Frankfurt, and Paris.

Forster Visits Havana Francis M. Forster, AAN vice president and dean of the Georgetown University School of Medicine, recently returned from Cuba where he addressed the First National Congress on Psychiatry and Neurology in Havana (January 26-30) and presented a paper on temporal lobe seizures. He also participated in a discussion on basic education as related to neurology and psychiatry. As past president of the American League Against Epilepsy, he discussed the subject of diagnosis and treatment of seizures before the Cuban League Against Epilepsy, using this occasion also to present a summary of the development and growth of the American league. On the social side, he reports a most enjoyable evening spent with Mrs. Forster in the home of Prof. and Mrs. Guiral, who is a frequent visitor to the U. S. and was an intimate friend of the late Foster Kennedy.

Gordon Seger Becomes NINDB Grants Chief Dr. Gordon H. Seger, formerly medical science research coordinator of the Office of Public Health Research Projects and more recently executive officer of the National Cancer Institute in Bethesda, has assumed the post of chief of extramural programs of the National Institute of Neurological Diseases and Blindness. He succeeds Dr. Edward P. Offutt, Jr., who has accepted a position as executive secretary of an important study section in the division of research grants, NIH.... The position of chief of extramural programs, NINDB, was originally held by Dr. Frederick L. Stone, who now is assistant for professional services to the vice-chancellor, Schools of the Health Professions, University of Pittsburgh.

Perlstein Course in Neuromuscular Disorders A course in the neuromuscular diseases of children with special emphasis on cerebral palsy will be offered by Dr. Meyer A. Perlstein at the Cook County Graduate School of Medicine in Chicago (June 20-July 1). This is an intensive two-week didactic and clinical course in the diagnosis and management of the neuromuscular diseases of children with special emphasis on cerebral palsy, and includes field trips to local clinics. Registration, which is limited, may be made by applying to the Registrar, Cook County Graduate School of Medicine, 707 South Wood Street, Chicago, Ill.

* * * * * *

New Construction Bills in House and Senate Two new bills, H. R. 3459 and S. 849, authorizing $30 million annually for three years to stimulate building and equipping of laboratories in medical schools, hospitals, and other nonprofit institutions, have been introduced in the House and Senate. S. 849 is

cosponsored by Senators Lister Hill (Democrat, Ala.) and Styles Bridges (Republican, N. H.), while a companion bill in the House, H. R. 3459, was introduced by Representative J. Percy Priest (Democrat, Tenn.). Prospective beneficiaries are schools of medicine, dentistry, and osteopathy. Federal construction grants for these purposes could be made up to 50 per cent of the project's total cost.... According to the Washington Report on the Medical Sciences, February 7, 1955, No. 399, "Chances of passage of these bills are good." Hill and Priest are chairmen of their respective committees that will consider the plan; Hill and Bridges are influential members of the Senate committee which would pass on money allocation. "....Hill-Bridges-Priest bill's purpose is to fortify statutory sanction and clarify objective for all chronic and killing diseases, not just heart disease and cancer."

Here and There On February 8 the St. Louis Society of Neurology and Psychiatry sponsored a lecture by Dr. Wilder G. Penfield of the Montreal Neurological Institute on the subject "Cerebral Pathology and Epileptic Seizures."... The third annual scientific meeting of the Houston Neurological Soicety was held March 18 and highlighted a symposium on hypophysial interrelationships.... The National Rehabilitation Association will hold its annual meeting at the Traymore Hotel in Atlantic City (May 16-17).... Dr. Samuel Brock, professor of neurology at New York University Postgraduate Medical School, served as moderator on a panel on Parkinson's disease at the New York Academy of Medicine (March 4). Among the participants were Kate C. Constable, Irving S. Cooper, and Lewis J. Doshay.... The 1955 officers of the medical advisory board of the Myasthenia Gravis Foundation are: chairman, Henry R. Viets; vice-chairman, George D. Gammon; secretary, Robert S. Schwab; and assistant secretary, Kermit E. Osserman.... Correction to be made in the February Newsletter: Kenneth Appel is no longer president of the American Board of Psychiatry and Neurology, as stated in the Newsletter. Dr. Appel has been succeeded by the current president, Bernard J. Alpers....

Paul Bailey

Neurology

BOOK REVIEWS

Neuro-Ophthalmology

Donald J. Lyle, M.D., F.A.C.S. Second edition, 1954. Springfield, Ill.: Charles C Thomas, Publisher. 591 pages, $17.50.

THE greatly expanded second edition of this well known treatise on the neurology of the eye follows the general plan of organization of the first edition. The first and somewhat longer section is devoted to a detailed consideration of the anatomy and physiology of the nervous system as it relates both directly and indirectly to the visual function and the motility of the eye. This involves a systematic account of the visual system from retina to visual cortex, the motor and sensory innervation of the eye and its appendages, mesencephalic and other brain stem reflexes acting upon eye movements and postures, their control by supranuclear mechanisms, and the autonomic supply to ocular muscles, glands, and blood vessels. Added to this are chapters on the auditory nerves and their interrelationships with ocular adjustments, on the arterial and venous supply of the brain, the eye and the orbit, and on the cerebrospinal fluid.

There is represented here an imposing compilation of facts culled from both older standard sources and the contemporary literature. The material is not always presented with the critical discernment or the clarity of exposition that one might wish. There is a good deal of unevenness in the treatment of various topics. For example, the sections on oculogyric mechanisms, the ocular reflexes, and the arterial and venous circulation of the brain are well done, but when the author comes to deal with such matters as the aphasias one senses that he is on unfamiliar ground.

The latter portion of the book is concerned almost entirely with clinical pathologic descriptions of cerebral disease, including chapters on acute infections of brain and meninges, neurosyphilis, demyelinating diseases, head injury, intracranial hypertension, and tumors of retina, optic nerves, and brain. Therapy is touched upon nowhere. One wonders why no mention is made of those diseases in which the changes in the eye itself are an integral part of the neurologic disorder and often give the leading diagnostic clue, for example, the corneal ring in hepatolenticular degeneration, the retinal and macular changes in the cerebral lipoidoses, the hazy cornea in gargoylism or the uveitis of sarcoidosis.

A final chapter presents brief descriptions of a list of neurologic syndromes of which ocular symptoms are a part. The general plan of the book has the disadvantage of lengthening it unduly because of repetition and the inclusion of a great deal of material extraneous to the subject at hand. It may be said, indeed, that the work is not properly a monograph at all, but rather a textbook of neurology apparently designed especially for the instruction of ophthalmologists. Nevertheless there is much in it that will interest neurologists as well, not the

least of which is the abundance of excellent illustrations. These include a large number of the author's original drawings and diagrams as well as photographs from the collections of the Cincinnati group of neurologists and neurosurgeons.

The book is handsomely printed with attractive page format and excellent reproduction of the illustrations.

R. B. R.

Psychology as a Profession

Robert I. Watson. 1954. Garden City, N. Y.: Doubleday and Company, 65 pages, 95 cents.

THE EFFORTS of a profession to achieve independence that comes with maturity is reflected in its history and the products of its growth process. Robert I. Watson has succeeded in capturing the tenor of this development, reflecting the experiences of a seasoned psychologist who has contributed to the academic, research, and applied aspects of psychology.

This book is not an attempt to present only the bright side of the picture of psychology as a field of professional endeavor. Watson recognizes and faces the problems that are concomitant with maturation and stabilization of a relatively new area of investigation and application. These matters are frankly discussed in two sections on unresolved intraprofessional issues and unresolved interprofessional issues.

The crux of the current struggle for status is dramatically, completely, and constructively related in his presentation of the unresolved interprofessional issues. The major contention is with medicine and involves the practice of psychotherapy in an unfettered atmosphere. The arguments of the psychiatric profession against licensure of psychologists in this activity are well known. On the other hand, a remarkably unemotional case is made by Watson in his review of this particular area of the psychologist's total function.

There are many psychologists who do not approve of independent practice by their own colleagues, especially in the field of psychotherapy – and Watson points out this conflict both within and outside of the profession. But, as he writes, "Psychologists are in independent practice. There is a demand for service and they feel they are serving a useful and worthy need by meeting this demand." The American Psychological Association and the American Board of Examiners in Professional Psychology are not opposed to independent practice by psychologists. The Group for the Advancement of Psychiatry is opposed to the practice of psychotherapy by psychologists with "psychiatric" patients. This group is joined by individual psychologists and by that section of the psychologic universe represented by the *Ad Hoc* Committee on the Relation of Psychology to the Medical Profession of the American Psychological Association.

Lest the reader believe that taking a position with regard to this question is a facile matter, he must wend his way around the maze of points of view presented in this book. Surely he will be impressed by Watson's plea to all sides of the question of private practice: "Clarification of our differences and a seeking for accord are essential. It is imperative that we do so as rapidly as possible because the greatest sufferer is neither the psychologist nor the psychiatrist. He who loses by our delay is the source of and inspiration of our work – the patient."

In summary, this book is a definite contribution to the understanding of psychology as a scientific discipline and as an applied professional field. For Doctor of Medicine and Doctor of Philosophy candidates this book should be required reading.

ROBERT M. ALLEN, Ph.D.
Professor of Psychology
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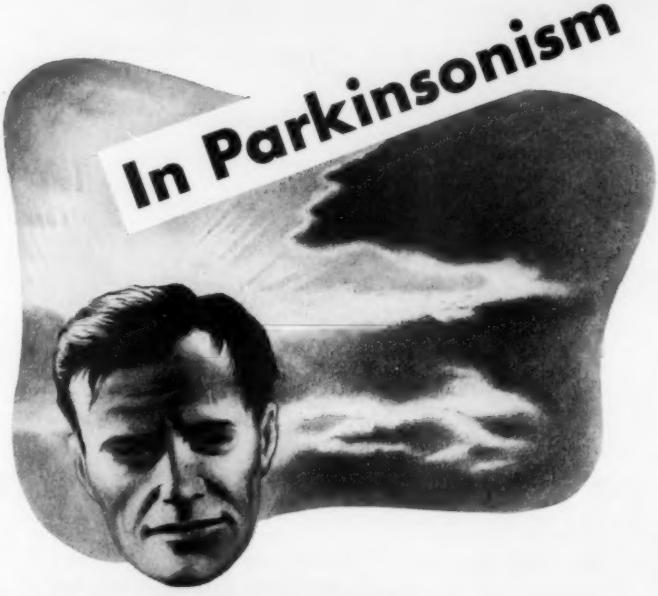

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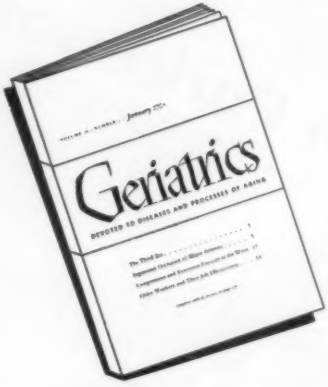

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WHO IS THE GERIATRIC PATIENT

One out of every three Americans is, or at any moment may become, a geriatric patient. More than 50,000,000 men and women are now over 45 years old.

Many of the problems which confront the neurologist today belong to the field of geriatric medicine. To round out the total clinical picture of your patient over 45, it is essential to keep abreast of the latest developments in geriatrics. For best and most complete coverage of this rapidly growing field, read GERIATRICS, the journal devoted to research and clinical study of the diseases and processes of aging.

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Products and Services

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This balanced nutritional supplement for prophylaxis or treatment of vitamin-mineral deficiencies, Maxilets, contains 10 essential vitamins (including natural B-complex factors), nine important minerals and trace elements and three hematinic factors. The proportion of minimum daily requirements provided per tablet is: vitamin A 2½ MDR; vitamin D 2½ MDR; vitamin B_1 5 MDR; vitamin B_2 2½ MDR; vitamin C 3 MDR; iron 1 MDR; iodine 1½ MDR. Tiny compressed tablets, Maxilets are stable, can't leak and won't stick together in the bottle. The prophylactic dose is 1 tablet daily. More may be prescribed by the physician for severe deficiencies.

MEBAROIN ELIMINATES SEIZURES IN 8 OF 15 GRAND MAL PATIENTS

In a study of 15 cases of grand mal epilepsy, the seizures of eight patients were completely eliminated, and the incidence reduced in four others, following treatment with the drug Mebaroin. Designed to treat convulsive disorders by a combination of therapeutic agents, Mebaroin contains diphenylhydantoin and Mebaral, the latter being a sedative with strong anticonvulsant activity and extremely low toxicity. Mebaroin is manufactured by Winthrop-Stearns Inc., New York City. Only three of the 15 cases failed to respond to Mebaroin. All patients in the study had histories of a minimum of one grand mal seizure per week for periods ranging from five to 15 years. Eight experienced no fruther seizures during the period of treatment and follow-up observation; one patient reported a single seizure; and three patients had a fewer number of seizures.

Dosage varied from one tablet twice a day to two tablets four times a day. None of the 12 patients who benefited from treatment experienced any side effects, a summary of the results discloses. Drowsiness observed in one patient disappeared when the dosage was reduced.

OLD "HERBALL" ON JUNIPER PLANT FEATURED IN DIURETIC REVIEW

The juniper shrub's flavorful blue berries were once believed to have a diuretic effect. In early America the juniper berries' oil also

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attracted interest by providing the flavor for gin. This usefulness has lasted.

The juniper is featured as the second of a new series being published in Diuretic Review, the scientific publication distributed to the profession by Lakeside Laboratories, Inc. of Milwaukee. The series is called "The Diuretick Herball." It revives descriptions and illustrations of plants used in olden times to induce diuresis. Pictures and texts are taken and adapted from early pharmaceutical "herballs" or published collections.

An early American herbalist, Jacob Bigelow, published one on the juniper almost 150 years ago. Diuertic Review's editors worked from it. Common juniper is in the Pinaceae or pine family. A shrub or small tree, it grows in dry soil from Maine to Maryland and westward to Manitoba and Illinois. "The volatile oil expressed from the berries, taken alone or as a constituent of gin, is a stimulant diuretic," the herball stated.

Three old alchemy symbols are used in the logotype of "The Diuretick Herball." The triangle represented water, the circle salt, and the square urine. Asparagus, first plant featured in the new series, was inspired by an herball published in Europe in 1562. The juniper is thus the first from an early American herball.

READY-TO-TAKE TETRACYCLINE SUSPENSION MARKETED BY UPJOHN COMPANY AS PANMYCIN

Panmycin Readimixed, a citrus-flavored oral suspension of the broad spectrum antibiotic tetracycline, is now being marketed by The Upjohn Company, Kalamazoo, Michigan. The Panmycin product, bottled as a liquid suspension stable for eighteen months, offers the physician something which he can prescribe with the knowledge that the pharmacist has been freed of any need for manipulation of the drug before dispensing.

Supplied in 30 cc. bottles, each teaspoonful of Panmycin Readimixed provides 250 mg. of tetracycline hydrochloride. Recent medical reports indicate that tetracycline is more stable, more readily absorbed into the blood stream, and causes fewer side reactions than older broad spectrum antibiotics.

The new oral suspension, made possible by a special coconut oil vehicle, is said to be free flowing, smooth, and of a pleasing golden color. Advantages of the oral suspension of Panmycin include greater acceptability to children and sometimes adults, and greater flexibility of dosage than can be obtained with capsules.

Clinical reports published thus far indicate that tetracycline is effective against more than

both patient and physician

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NEW SPINAL ANESTHETIC CALLED SAFE AND VERY RAPID-ACTING

Sympocaine, a new anesthetic under clinical study by Winthrop-Stearns Inc., New York City, has been found to be one and one-half times more potent than Pontocaine (tetracaine) very rapid in action and relatively non-toxic when administered spinally. Spinally, the average duration of analgesia with Sympocaine was found to be approximately two and one-half hours when an 0.5 per cent hyperbaric solution without epinephrine was used. The duration was prolonged to three hours when epinephrine was employed, with no increase in the incidence of side reactions. In isolated cases, "six hours or longer" of analgesia were observed.

Animal and clinical tests indicate Sympocaine to be as fast-acting as any present anesthetic, average onset time ranging from 1.1 to 2.0 minutes. Referring to side effects, investigators found hypotension to be the most common and "more frequent in the high than in the low spinals."

NEUROSURGICAL INSTRUMENTS

PUTNAM VENTRICULOSCOPE

Hydrocephalus may be arrested by the removal of the choroid plexus. This operation may be accomplished by coagulation of the tissue while it is surrounded by the cerebrospinal fluid. The instrument consists of a rod of optical glass ground to form lenticular surfaces at the ends. At the lower end are carried an electric lamp and two electrodes connected to a radio frequency electro-surgical unit. Clear vision is possible throughout the operation.

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*Beckman, H. *Treatment in General Practice* (Saunders) 1948.

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CLINICAL DATA ON REQUEST

*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

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